ST. FRANCIS HOSPITAL ISSUE

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SYMPOSIUM ON CANCER

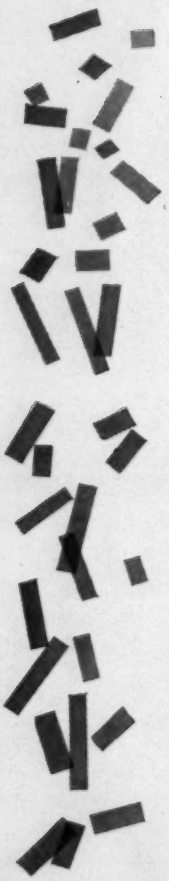
Complete Contents on Page iv

Program, Annual Meeting D.A.G.P. page 291

FOR PERSISTENT INFECTIONS

CHLOROMYCETIN®

COMBATS MOST CLINICALLY IMPORTANT PATHOGENS



Acquired resistance seldom imposes restrictions on antimicrobial therapy when CHLOROMYCETIN (chloramphenicol, Parke-Davis) is selected to combat gram-negative pathogens involving enteric and adjacent structures of the urinary tract. The acknowledged effectiveness with which CHLOROMYCETIN suppresses highly invasive staphylococci[1-9] extends to persistently pathogenic coliforms.[6,10-15] Experience with mixed groups of Proteus species, for example, "...shows chloramphenicol to be the drug of choice against these bacilli...."[15]

CHLOROMYCETIN is a potent therapeutic agent and, because certain blood dyscrasias have been associated with its administration, it should not be used indiscriminately or for minor infections. Furthermore, as with certain other drugs, adequate blood studies should be made when the patient requires prolonged or intermittent therapy.

REFERENCES:

(1) Petersdorf, R. G.; Bennett, I. L., Jr., & Rose, M. C.: *Bull. Johns Hopkins Hosp.* 100:1, 1957. (2) Yow, E. M.: *GP* 15:102, 1957. (3) Altemeier, W. A., in Welch, H., and Marti-Ibanez, F., ed.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 629. (4) Kempe, C. H.: *California Med.* 84:242, 1956. (5) Spink, W. W.: *Ann. New York Acad. Sc.* 65:175, 1956. (6) Rantz, L. A., & Rantz, H. H.: *Arch. Int. Med.* 97:694, 1956. (7) Wise, R. I.; Cranny, C., & Spink, W. W.: *Am. J. Med.* 20:176, 1956. (8) Smith, R. T.; Platou, E. S., & Good, R. A.: *Pediatrics* 17:549, 1956. (9) Royer, A.: Scientific Exhibit, 89th Ann. Conv. Canad. M. A., Quebec City, Quebec, June 11-15, 1956. (10) Bennett, I. L., Jr.: *West Virginia M. J.* 53:55, 1957. (11) Altemeier, W. A.: *Postgrad. Med.* 20:319, 1956. (12) Felix, N. S.: *Pediat. Clin. North America* 3:317, 1956. (13) Metzger, W. I., & Jenkins, C. J., Jr.: *Pediatrics* 18:929, 1956. (14) Woolington, S. S.; Adler, S. J., & Bower, A. G., in Welch, H., and Marti-Ibanez, F, ed.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 365. (15) Waisbren, B. A., & Strelitzer, C. L.: *Arch. Int. Med.* 99:744, 1957.

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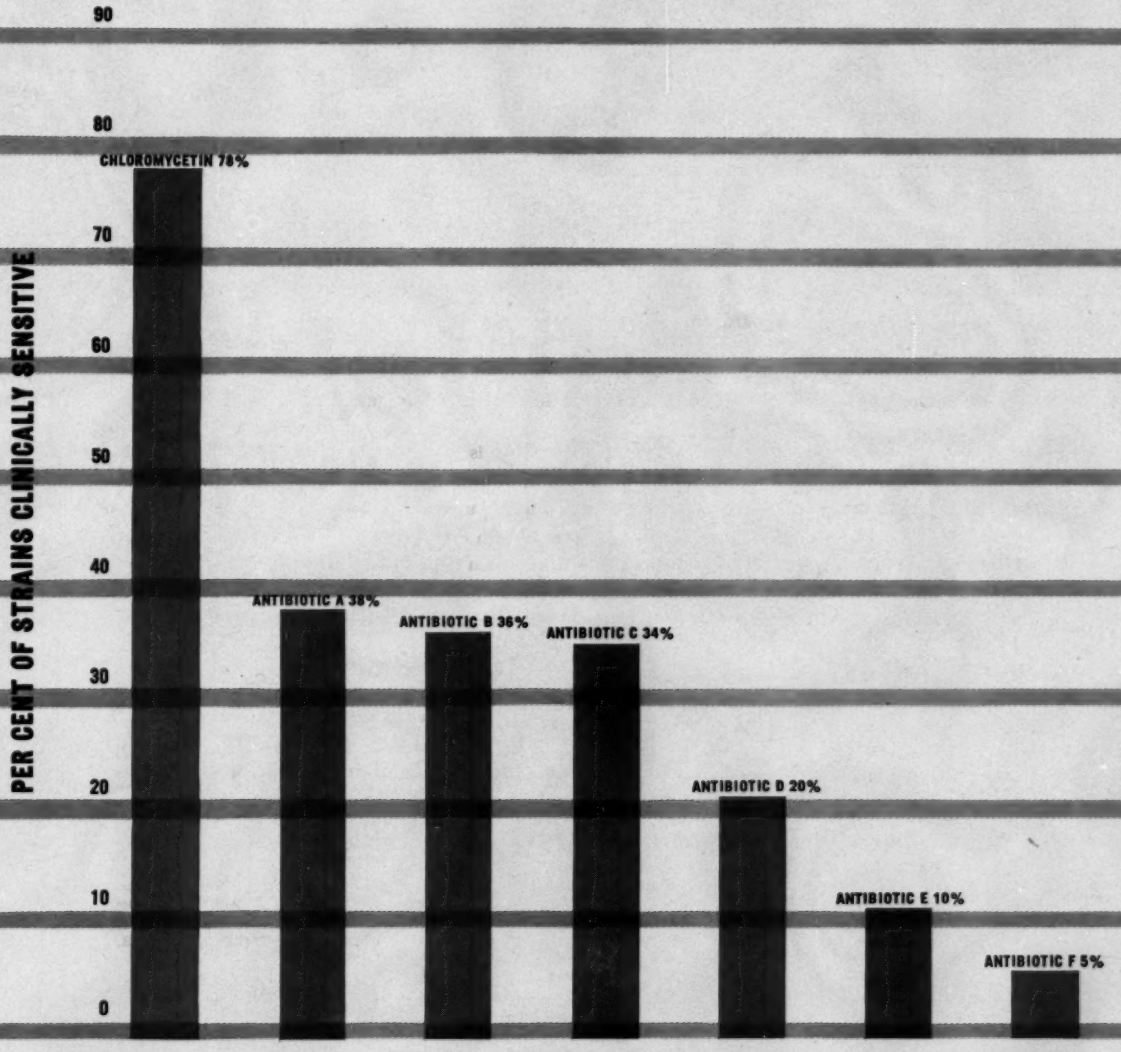
50168

COMPARATIVE SENSITIVITY OF MIXED PROTEUS SPECIES TO CHLOROMYCETIN AND SIX OTHER WIDELY USED ANTIBIOTIC AGENTS*



*This graph is adapted from Waisbren and Strelitzer.[15] It represents *in vitro* data obtained with clinical material isolated between the years 1951 and 1956. Inhibitory concentrations, ranging from 3 to 25 mcg. per ml., were selected on the basis of usual clinical sensitivity.

DELAWARE STATE MEDICAL JOURNAL

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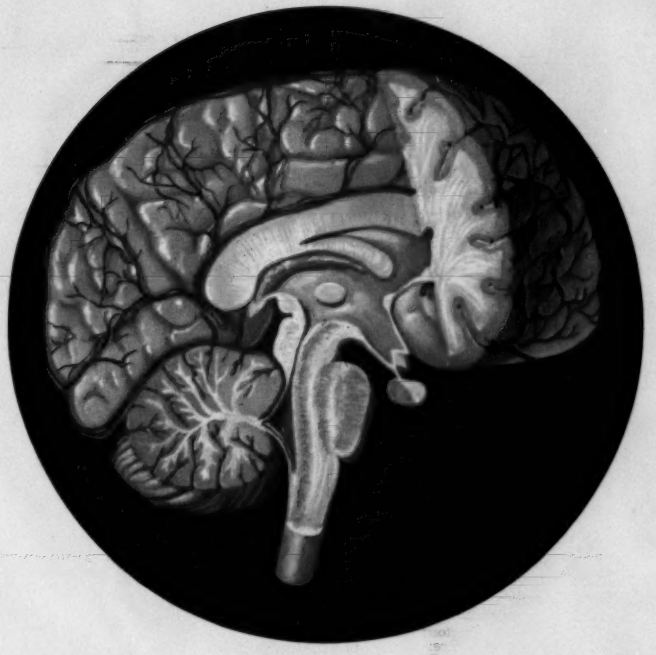

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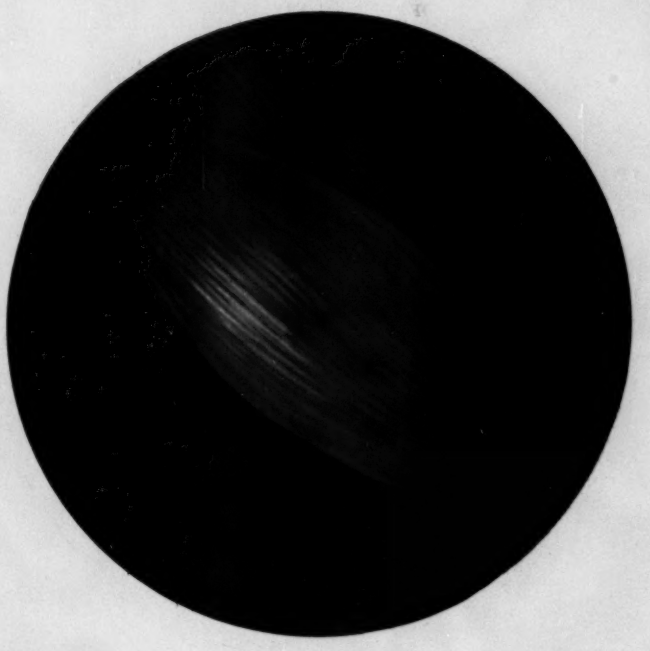

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Lewis, H. H.: Frumess, G. M., and Henschel, E. J.: Rocky Mountain M. J. *54*:806 (Aug.) 1957.

"Results of treatment with oleandomycin-tetracycline of 50 infections [mostly respiratory] due to resistant organisms and 40 infections [respiratory, skin, urinary infections] due to sensitive organisms are very encouraging. In some of these patients, [Signemycin] was lifesaving, and in others surgery was made unnecessary. This confirms other reports."

Shubin, H.: Antibiotic Med. & Clin. Therapy *4*:174 (March) 1957.

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Levi, W. M., and Kredel, F. E.: J. South Carolina M. A. *53*:178 (May) 1957.

Of 50 patients with various infectious processes, 26 had not responded to previous antibiotic therapy. With Signemycin "Ninety-six per cent of the mixed infections were clinically controlled. . . . and in none of the cases was there any reason to discontinue the drug."

Winton, S. S., and Chesrow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55.

Signemycin in 79 patients with severe soft tissue infections: "The average response of these cases was excellent and inflammatory symptoms subsided with almost uniform rapidity....The magnitude and incidence of surgical intervention was reduced....Side reactions were minimal. . . ."

LaCaille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67.

Five groups of patients (total 211) with acne were treated with one of five antibiotic agents, including Signemycin (55 cases). "The results were evaluated taking into consideration the usual response to such conservative conventional therapy and the rapidity of response." In 8 weeks, Signemycin rapidly attained and maintained the highest percentage of efficacy of antibiotic agents tried.

Frank, L., and Stritzler, C.: Antibiotic Med. & Clin. Therapy *4*:419 (July) 1957.

In the treatment of 78 patients with tropical infections, some complicated by multiple bacterial contamination or present for years, Signemycin was found to be "...an exceptionally effective agent," requiring smaller doses and less extended periods of therapy than with the tetracyclines alone, and "caused no notable toxic reactions."

Loughlin, E. H., and Mullin, W. G.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.

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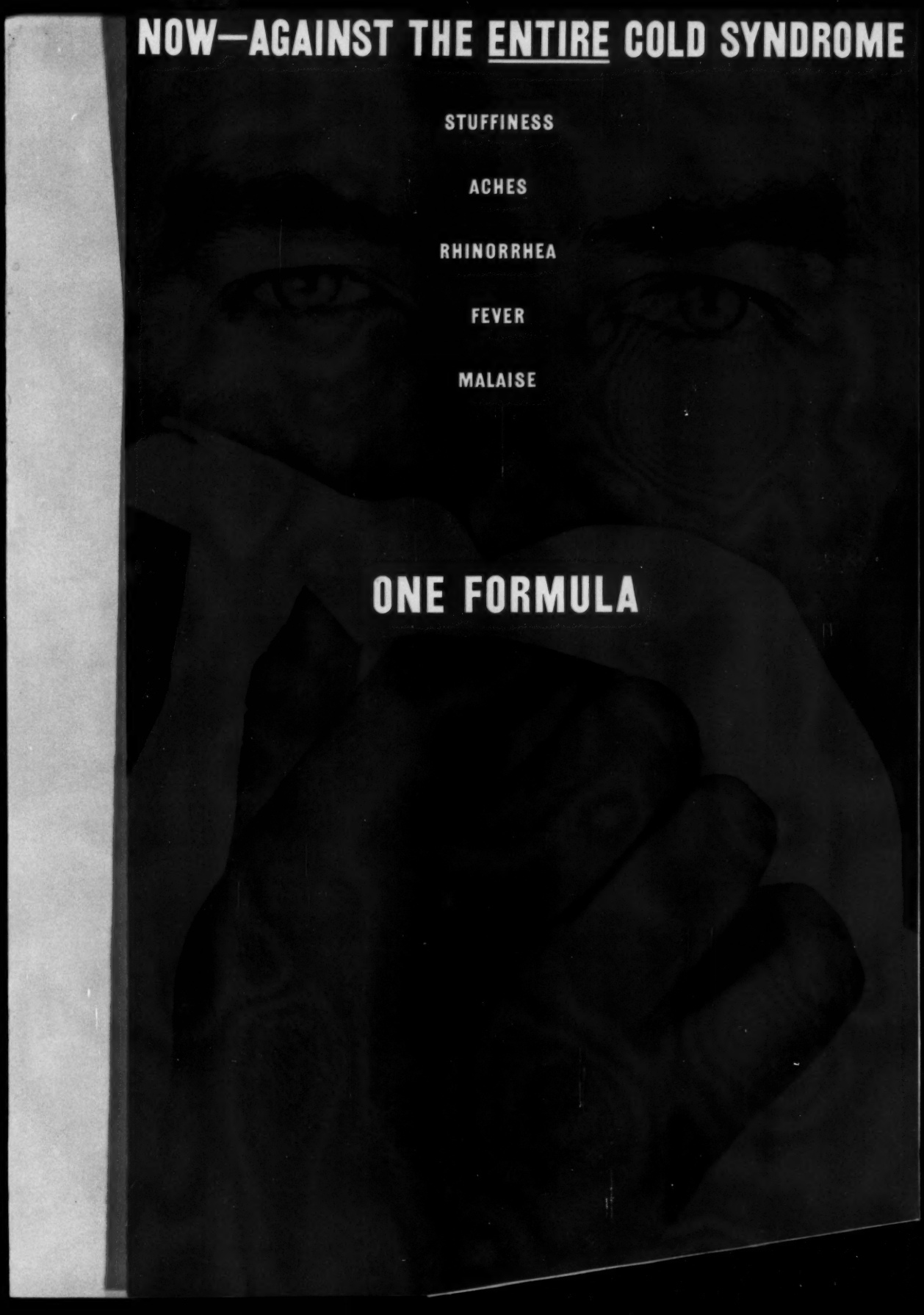
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symptomatology "across the board"; and

PRACTICAL because the average
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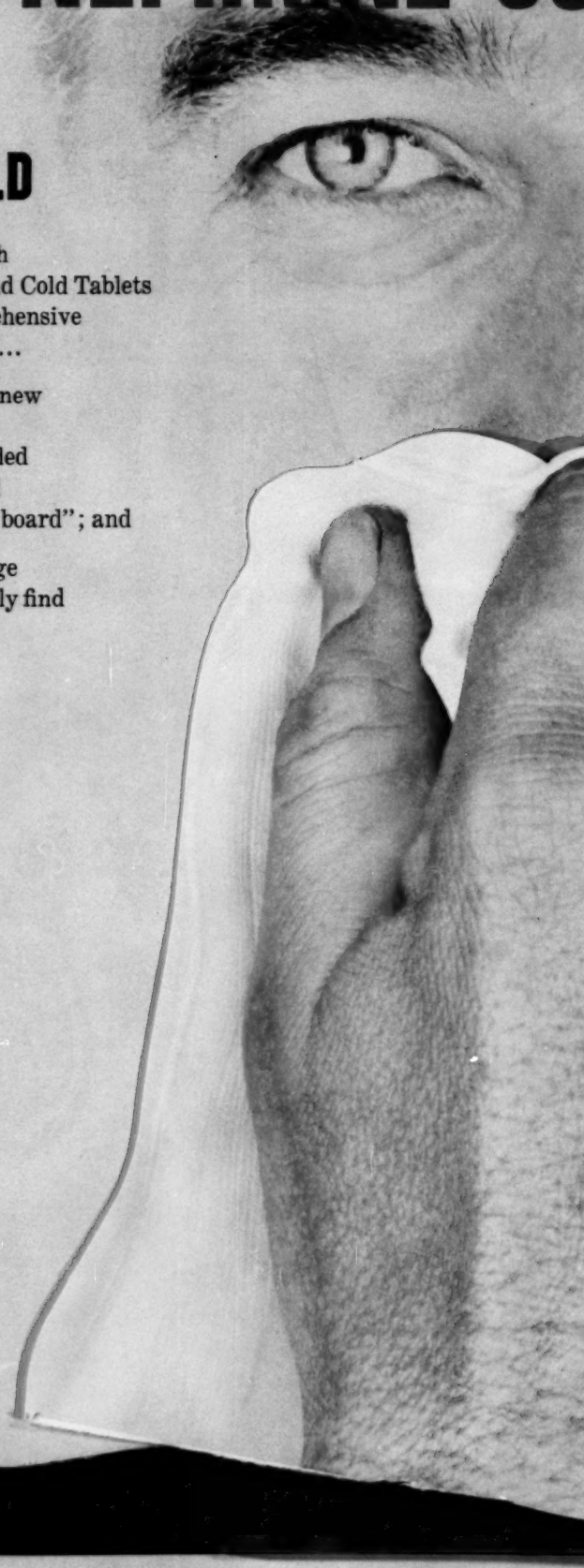

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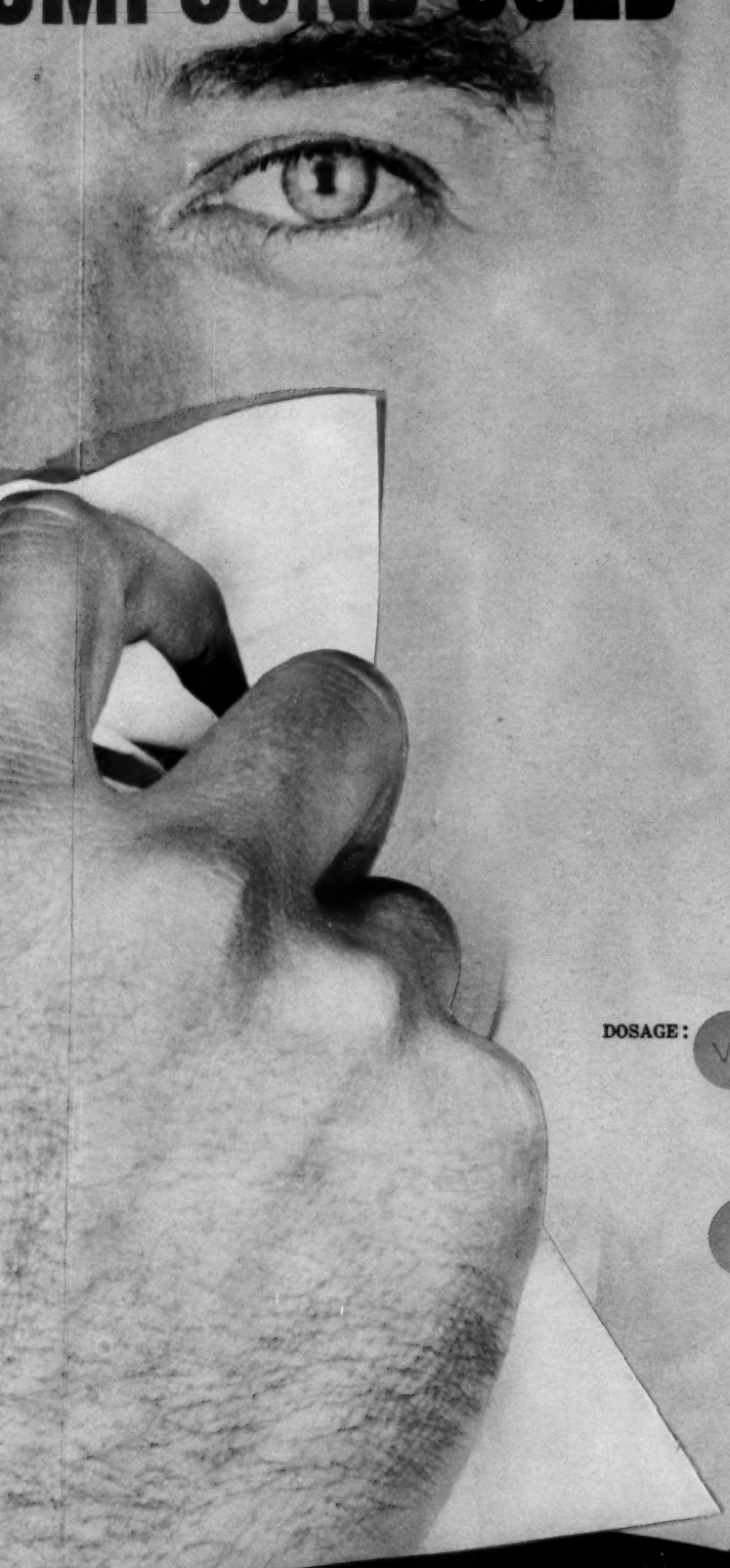

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modern analgesic and antipyretic

vs. Rhinorrhea—
Thenfadil® hydrochloride ...7.5 mg.
effective, well-tolerated antihistaminic

vs. Lassitude, Malaise—
Caffeine...15 mg.
dependable, mild, stimulating agent

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Children 6 to 12 years—
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Bottles of 100 tablets

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COMPREHENSIVE because this new preparation rationally combines drug actions needed to control common cold symptomatology "across the board"; and

PRACTICAL because the average patient will promptly find relief from his distress.

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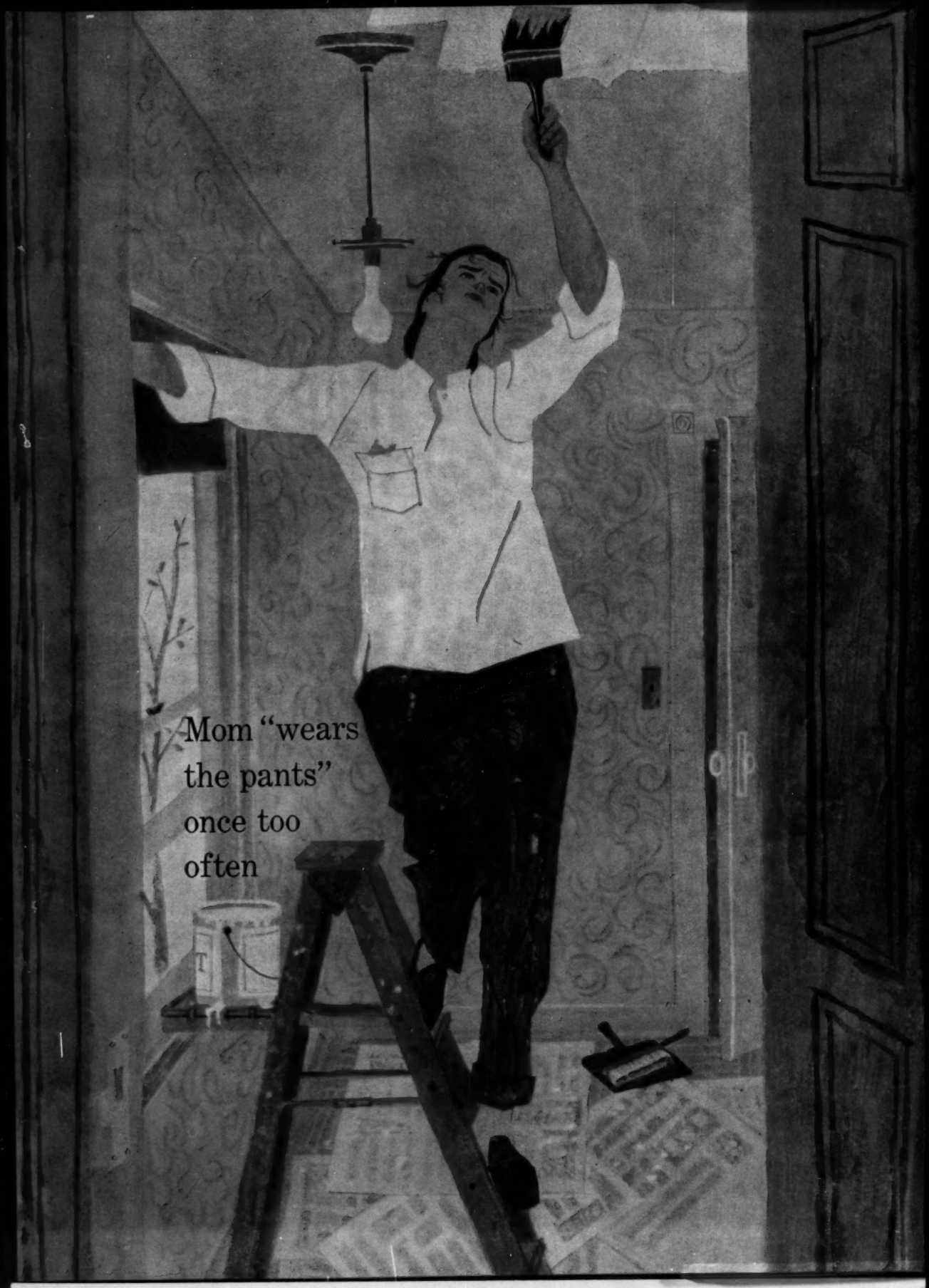
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the pants"
once too
often

frozen shoulder

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Dried milk .....4 tbsp.
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Karo .....½ oz.
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FORMULA III .....16 cals./oz.
Whole milk .....10 oz.
Water .....10 oz.
Karo ..... 1 oz.
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FORMULA III .....20 cals./oz.
Evap. milk ..... 6 oz.
Water .....12 oz.
Karo ..... 1 oz.
3 oz. x 6 q 4h.

FORMULA III .....18 cals./oz.
Dried milk .....6 tbsp.
Water .....20 oz.
Karo ..... 1 oz.
3½ oz. x 6 q 4h.

FORMULA II .....13.5 cals./oz.
Whole milk ..... 9 oz.
Water .....11 oz.
Karo .....¾ oz.
3½ oz. x 6 q 4h.

FORMULA II .....16 cals./oz.
Evap. milk ..... 5 oz.
Water .....13 oz.
Karo .....¾ oz.
3 oz. x 6 q 4h.

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Dried milk .....5 tbsp.
Water .....20 oz.
Karo .....¾ oz.
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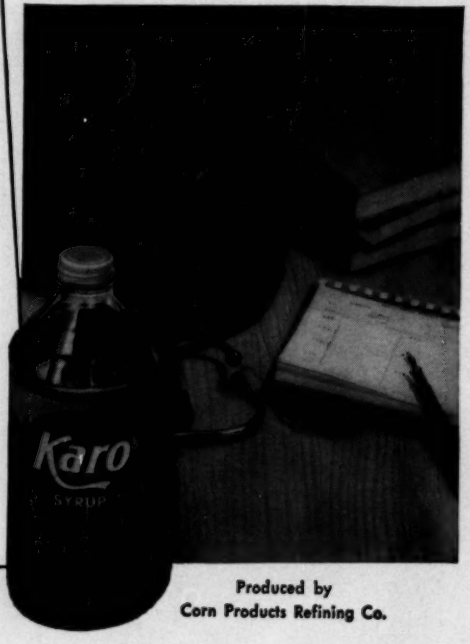

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Hydrocortisone (alcohol)	2.5 mg.
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Asiatic Virus Raises Threat
Government Buys, Prods
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New York, Aug. 15 (AP) Laboratory tests on e foreign exchange student arrived Aug. 8 show they victims of Asiatic flu, the health department repo today. The eight arrived plane from Europe.

Twenty-nine other stud suffering from influenza rived Tuesday from Ro dam on the ship Arosa Sky. One, Nicholas Memmos, Greek exchange student, die yesterday. Six of these students were released today the others are to be re tomorrow. It has not termined whether died from Asiatic

Pea vac izat flo the ority States

THE INFLUENZA

How Deadly Will it Be? W
What Can We Do about It?

IF YO

Answers A

A new illnes —is showing u around the worl now have appe

e War on Mutant A

f Florence was in the grip of an epi- nic of colds, coughs and fevers, astrolo- s . . . declared that it was caused by influence of an unusual conjunction of nets. This sickness be known as "infl

—Chronicles of 1200-1470.

To combat new r nce," a worldwide week in respons m the Far East. St he World Health a, which collects i m around the globe cimens of the ene s. In more than a uding those of th

Asian Flu: the Outlook

Asian influenza will hit the U.S. this fall before mass immunization can be effective, and the nation faces an epidemic which may strike 15 million to 30 million people. The disease is relatively mild (in no way comparable to the killing "Spanish flu" of 1918-19), and is likely to cause only a small number of deaths among the feeble young and enfeebled old. But it may compel 10% to 20% of the population in affected areas to tak thus

W quie a co pect Ser pop

U.S. Fighting Asia

The War On Asiatic Flu

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PUBLIC HEALTH

Influenza May

➤ INFLUENZA, one of the most unpredictable of communicable diseases, is resting "on cat feet" across the nation right now. It has already struck once this year in mild epidemic form at an Air Force base in Colorado. When and how severely it will strike again is a perennial riddle to public health authorities.

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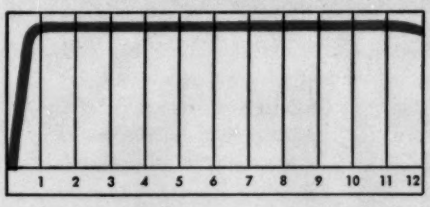

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CARCINOMA OF THE ESOPHAGUS

FRANK T. O'BRIEN, M.D.

"Too little, too late!" so frequently is the story regarding the diagnosis and treatment of carcinoma. This is doubly true in the case of esophageal cancer. What can we do in an attempt to correct this situation?

Many times the original complaint in the history will point to the offending lesion. It is of importance that the patient's statements be accurately evaluated, keeping in mind the possibility of malignant disease. The patient with dysphagia frequently adds "red herrings" to dissuade the physician from a logical train of subsequent studies. A few of these include: 1.) neurotic tendencies, 2.) emotional insecurity, 3.) hysteria —globus hystericus, 4.) "nervous stomach", 5.) indigestion, 6.) specific food allergy, 7.) poor dentures, 8.) overwork, 9.) sinusitis with "post-nasal drip", 10.) drinking bouts and excessive smoking. There is, no doubt, a host of others. To maintain the original study plan for diagnosis in such cases is sometimes difficult and as a result, time is wasted. The patient who, earlier, may have had a chance for a *cure* becomes a possible candidate for a palliative procedure.

The salvage rate for carcinoma of the esophagus is very low. This should not be a rule of thumb for treating a patient as a statistic; every case must be evaluated on its merits. The shrunken, emaciated, poor risk individual, oftentimes has a resectable neoplasm. If the first examining physician considers the possibility or at least has a suspicion of carcinoma and follows through with a barium swallow and esophagoscopy, the five year survival rate for carcinoma of the esophagus would not be so appallingly low. The patient with dysphagia should be investigated immediately. Delay results in a regrettable outcome.

The case in point is that of a 73 year old white man who presented himself to his family physician in September, 1956, because of dysphagia and regurgitation after swallowing. He was hospitalized September 6, 1956, for evaluation. The history dated back four months prior to admission when he noted that solid foods would occasionally "stick in his gullet". This condition seemed to get progressively worse until admission at which time all foods had to be semi-liquid. He suffered no pain, but thought he might have lost some weight. Physical examination revealed an elderly, thin, white male in no distress. All findings were within normal limits except for poor oral hygiene, liver palpable one finger breadth below the right costal margin, and a right inguinal hernia—maintained in reduction by a truss. (This had been present for 30 years.) His hemogram showed a 79% hemoglobin, RBC 3.8 million, WBC 10,150 with a normal differential count. His hematocrit was 42%.

On x-ray examination, the patient was given a barium capsule which passed to a point just below the arch of the aorta where it remained in a relatively fixed position for a period of time, then dissolved and passed into the stomach. He was given thick barium paste to outline the esophagus; this showed an obstruction below the arch of the aorta. The involved area measured 4 cm. in length. On the lateral film, the level of the obstruction was noted to be at the 7th thoracic vertebra. This is seen in Figure 1. Actually, it is between the 7th and 8th thoracic vertebrae. Chest films, both PA and lateral views, showed the diaphragms to be at normal levels.

On September 10th, an esophagoscopy was performed; this revealed complete ob-

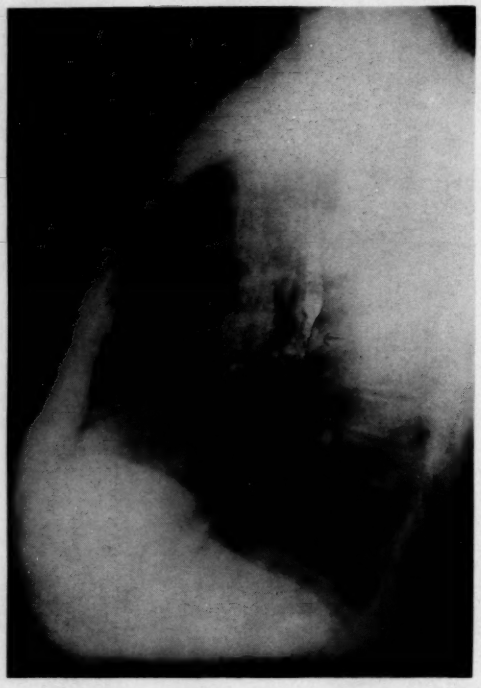

FIGURE 1
Barium Swallow performed on a 73-year-old white male. Obstructing esophageal carcinoma pointed out in the middle third of the esophagus.

struction approximately 30 cm. from the superior alveolar ridge. From this site, a biopsy was taken of protruding mucosa; no definite tumor mass could be visualized. The microscopic section of this tissue showed abnormal epidermoid cells, not conclusive of neoplasm.

Because of the persistence of the obstruction and the mounting evidence in favor of carcinoma, the patient underwent an esophagectomy on September 17, 1956. This was done via the right-sided approach, first opening the thorax and freeing up the entire esophagus to approximately four inches above the lesion, ligating the azygos vein and dissecting down the entire length of the thoracic esophagus to the hiatus. The patient was then turned and the abdomen entered. Some difficulty was encountered in mobilizing the stomach because the omentum was fixed in the right inguinal hernia. It was necessary to ligate the omentum, leaving a small portion of it in the hernia before continuing the mobilization of the stomach. The stomach was amputated from the esophagus and the esophageal-cardia junction closed. The stomach then was threaded through the diaphragmatic hiatus and brought up into the right chest, where it was anastomosed to the proximal esophagus four inches above the offending lesion.

Because of the ligation of both vagus nerves, it was necessary to keep a Levin tube in the stomach for approximately one week in order to prevent gaseous distention of the narrow thoracic stomach. The patient was discharged from the hospital on his tenth post-operative day. He was completely asymptomatic and was able to eat a regular diet without difficulty.

The pathological report on the tissue was epidermoid carcinoma of the esophagus. The tumor extended into the muscular coat, but did not, either grossly or microscopically, extend to the outer limits of the esophageal musculature or to the limits of the

FIGURE 2
Barium Swallow two weeks following esophagectomy. One stage subtotal esophagectomy performed via the right thorax and mid-abdominal routes. Patient asymptomatic one year post-operatively.

resection. It was thought that the resection was adequate. Figure 2 shows a post-operative barium swallow. The stomach is seen high in the chest.

One year post-operatively, the patient is doing well. He has no complaints referable to his operative site, no dysphagia; he has gained weight and has returned to his normal way of life. He still wears a truss for his right inguinal hernia. It is much too early to suggest a cure, but certainly his palliation has been rewarding.

This case is worthy of presentation because it points out that where there is no delay, the outcome is sometimes favorable. The fact that the time involved between his first visit to his local physician and his hospital discharge was less than thirty days, is an achievement worth recording, particularly for an individual in this age group.

DISCUSSION

The remarkable courage of the great surgeons who attacked this neoplasm can only be viewed with inspiration and respect. The names of Bilroth, Czerny, von Mikulicz and others are mentioned in the historical background. The first successful esophagectomy in this country was reported by Franz Torek in 1913. The patient was 69 years of age when she submitted to the extirpation of her entire thoracic esophagus. She died at the age of 83 of other causes. This particular operation has been revised and readvocated by Watson; instead of leaving an esophageal fistula and gastrostomy, he fashions an anterior esophagus (substernal) using the right colon.[1] This type of procedure is comparable to that outlined by Lewis in 1946, for growths in the middle third of the esophagus.[2] The one-stage resection and reconstruction for growths of the mid-esophagus was thought feasible and was performed in this country by MacManus. In 1956, MacManus, Paine, Dunn, and Merdinger reported on 138 cases of carcinoma of the esophagus. Of this series, 115 were operated upon; 64 lesions were resected (55.6%); 15 patients died before leaving the hospital (23%); and 5 lived over five years.[3] This series included the cardia of the stomach which may have bolstered the survival rate. MacManus pointed out that "Our obligation to the cancer patient should not be confined to our efforts to cure him. Where cure may not be possible, palliation should be our goal and is often sufficient justification for a properly conceived and well executed operation." Thus the bypass operation using the right colon and leaving the inoperable carcinoma in situ may offer palliation that would otherwise be wanting.

The Tumor Registry of the State of Delaware reported thirty cases for the three year period of 1954 through 1956.[7] No study of statistical significance could be made from such a small series. Of the cases reported, the average age was 62 years. The ratio of males to females was almost equal.

Watson and Goodner reviewed 1250 cases from the Memorial Hospital in New York.[4] This covered a period from 1931 to 1955 (25 years). Only 17 cases survived five years or more. Seventy-seven cases received surgery alone with a 4% survival. 929 of the series received radiation alone with a 0.65% five year salvage rate. 39 patients received both surgery and radiation with a 7.7% five year survival. This report shows that carcinoma of the esophagus is not a rare disease, probably about 4% of all gastrointestinal malignancies. The upper third is involved in about 20% of cases, the middle third in 37% and the lower third in the remaining 43%. It occurs more frequently in males. This lesion seems to be increasing in women, however, and at the present time the ratio is 9 to 1. Involvement in women is usually in the upper third and the age group younger. (The author saw one female, age 34, with a tracheo-esophageal fistula due to carcinoma of the esophagus.)

DIAGNOSIS

A transient dryness or tickling in the throat frequently precedes minimal dysphagia. The suspicious physician when the patient first presents himself with dysphagia can prevent him from becoming another fatality through early study. A barium swallow and esophagoscopy should be considered early. Tissue biopsy by esopha-

goscopy is positive in 80% of these cases. The differential diagnosis must include:

1. Foreign body in the esophagus (meat, vegetables, etc.)
2. Tuberculosis of the esophagus (quite rare)
3. Luetic esophagitis (rare)
4. Plummer-Vinson syndrome (frequently anemia and other symtoms are present)
5. Extrinsic pressure (goiters, tumors of the trachea, tumors of the mediastinum, aortic ring)
6. Peptic esophagitis (common in emotional states)
7. Cardiospasm—achalasia
8. Diverticulum of the esophagus
9. Diaphragmatic hernia

Nakayama uses radioactive phosphorus to aid in the differential diagnosis of esophageal carcinoma.[8] He claims that 96% of cases could be diagnosed correctly by giving the patient radioactive phosphorus which is concentrated in the neoplastic cells. Then a definite response is measured by a counter which is inserted via gastric tube. Nakayama is a famous surgeon and will, no doubt, add a great deal to solution of this problem. (Esophageal carcinoma is most commonly found in the Japanese male.)

RESECTION

Whether or not the lesion is operable cannot be determined by esophagoscopy or x-ray so that most cases should have a bronchoscopic examination. Extension of the carcinoma into the surrounding structures makes resection impossible. Bronchoscopic examination may show an ingrowth of the tumor or a fistula from the esophagus. The presence of a Horner's syndrome, the destruction of a thoracic vertebra, metastatic deposits in the lung fields make for a poor prognosis. At the time of operation, fixation of the growth to the aorta, trachea or pulmonary vessels may deter all but a palliative procedure. This is also true when the liver, peritoneal cavity (Blumer's shelf) and abdominal lymph nodes are discovered to be involved.

This carcinoma occurs most commonly in the normally narrowed areas of the esophagus. Thus, trauma may play a part at the thoracic inlet, the aortic arch and at the diaphragm (outlet). The bolus of food seems to strike these three areas as it is propelled into the stomach. The type of carcinoma is either epidermoid or adenocarcinoma. Since the lower third is the common site of adenocarcinoma of the esophagus one cannot determine whether the growth originated in the stomach or from the esophageal glands of the lower esophagus.

Esophagectomy is indicated whenever a malignant lesion of the esophagus is found to be resectable. This should be performed regardless of the age, sex, or degree of inanition. If resection is impossible a bypass procedure should be planned for palliation. The ability to swallow affords much comfort to the patient.

SUMMARY

1. Carcinoma of the esophagus still carries a formidably high mortality.
2. Age and debilitation should not deter our surgical intervention.
3. The case of a 73 year old male was presented (asymptomatic one year postoperatively).
4. Historical note with other clinical statistics were presented.
5. Prompt investigation of *dysphagia* was stressed.

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THE DIAGNOSIS AND TREATMENT OF CARCINOMA OF THE CERVIX IN SITU*

RICHARD C. HAYDEN, M.D.,** MORTON KEYSER, M.D.,***
and JOSEPH W. ABBISS, M.D.****

DR. R. C. HAYDEN:

Carcinoma in situ of the cervix is one type of cancer that can be cured if detected and treated early. By definition, carcinoma in situ means localized cancer without invasion into the lymph glands, blood stream, or deeper tissues.

The histology of the cervix shows the basement membrane to be intact in carcinoma in situ. As long as this basement membrane is intact, even though you have all the criteria present here for malignancy, such as mitosis, hyperchromatosis, distortion of normal cell pattern, and so forth, you can still call that a carcinoma in situ, or carcinoma in place: it hasn't invaded. There are various names for it: interstitial carcinoma, Bowen's disease of the cervix, precancerous cervical lesion.

Once it has invaded through the basement membrane, it is invasive cancer. The main question in diagnosis: is this lesion actually a precancerous lesion or already invasive cancer? That is a debatable point between many cytologists, gynecologists and pathologists throughout the world. Actually, TeLinde and his group feel that it is a definite forerunner of actual invasive cancer. The average age that they've found carcinoma in situ is 35 years. The average age at which actual invasive cancer is present is about 45 to 49 years, so that there is usually a latent period of 10 years before a preinvasive cancer will develop into invasive cancer, if this hypothesis holds true.

Other men deny that there is any such relationship between carcinoma in situ and actual invasive cancer. The only way we can prove this point is to allow certain patients who have carcinoma in situ to be followed over a period of time and show that it does develop into a malignant or an invasive lesion. That would have to be 100% true to be accurate. Actually, that has been done by one doctor in Norway, who has found that 26% of the patients he has allowed to go along with the carcinoma in situ have eventually developed invasive carcinoma, after five and twelve years duration. Other men have found that it hasn't worked out this high while others have even higher results. He's the only individual who has carried over 100 patients along with carcinoma in situ.

Naturally, the majority of men will treat their patients definitively, rather than do any experimental work along this line. The question of what methods we have for diagnosis is very important. You are all familiar with the vaginal smear, the cytology method developed by Papanicolaou. This is extremely important in carcinoma of the cervix because it is the one place in the entire body where we can pick up a potentially malignant, or an actually malignant, lesion by cytological examination.

The main difficulty has been in past years that there are very few trained cytologists in this country. In other words, a man has to take years probably, just as he would in pathology, to be a cytologist. However, with the actual experience being improved every year, we're making more and more early diagnoses of cancer of the cervix, especially the carcinoma in situ.

There are different stages of the smears that are taken, and these are graded accordingly. Dr. Abbiss will probably speak about those. They run from Class I to Class V. It is not a 100% diagnostic meth-

* Symposium held at the St. Francis Hospital, March 19, 1957.
** Chief, Obstetrics and Gynecology.
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**** Pathologist.

od, and never should be because it is only a screening method. Let's say if we had a thousand women in this community who we wanted to run through for a test for cancer of the cervix, the vaginal smear or cytology smear would be an excellent method of screening the population. If they are positive, then further diagnostic methods should be used. One of the most important, and often neglected, has been the old Schiller test.

Schiller found that by staining the cervix with an iodine solution that he could show that the glycogens present would absorb the iodine and take a mahogany stain. Most of the cervix is rich in glycogen; however, where there is a cancer present, the mahogany stain is not taken up. However, that has been proved false: any erosion of the cervix, any leukoplakia or any disturbance of the glycogen content present in the cervix will not take up the mahogany stain. Nevertheless, its main value is that it will show you where to biopsy the cervix, and this test should be used routinely in cancer clinics today. The cervix is painted with iodine solution and then the biopsy is taken where the stain is shown not to be present.

Another diagnostic test of questioned value is colposcopy. Hinselman, in 1925, developed a colposcope, not a culdoscope, with which you can look into the vagina. It magnifies the vaginal contents, the cervix, and the surrounding structures. The main importance of a culposcope is that it magnifies between ten and twenty times, and you can see many areas where there are leukoplakic changes going on, where there are eroded changes, and where there might be vascular changes that are not visible to the naked eye. Most clinics have discarded this test; however, the Jefferson group is very enthusiastic about it and use it as an adjunct in diagnosis.

The only true method, of course, of diagnosing any cancer, whether it is in situ or invasive cancer, is by biopsy, and no individual biopsy is 100% accurate. When you take a cervical biopsy, you should include the whole squamo-columnar junction in a circular fashion, and it usually should be done with a cold knife, rather than a cautery, because of the destruction of tissues by the cautery. When you take a punch biopsy, and the diagnosis comes back "carcinoma in situ", don't rely on that. There may be invasive cancer present unless you take multiple biopsies and do fairly good serial sections.

Suppose you do have a malignant smear. Let us say it shows a Class IV or Class V, and the cervix looks perfectly benign. Then you must think of endocervical cancer, and many times in your office you can do an endocervical curettage. The cervix may look perfectly healthy and benign, but by taking a little tissue with a curette you can pick this up and it is the same as a cervical biopsy. It will give you an actual pattern of tissue that you can look at under the microscope after it has been stained, so that the endocervical biopsy, along with the actual biopsy from the squamous part of the cervix, is the important part in the diagnosis of cancer.

DR. J. W. ABBISS:

I am not quite sure what I should talk about because the gynecologists have already talked about nuclei, hyperchromatism, loss of polarity and invasion, so maybe I should talk about how to do a hysterectomy or some other such subject!

I think the subject of carcinoma in situ is a most fascinating one because here we are possibly — I do not say probably, or even certainly — looking at the earliest stages of cancer in an organ which is readily visible to us. I thought it would be interesting to illustrate some of the features of this particular lesion by making use of an actual case in my own recent experience and using some of the photo-micrographs taken from the material from this case.

I think one of the important things to remember about this type of lesion is the fact that it often occurs in a normal appearing cervix, or in one which shows what would ordinarily be considered to be a laceration or erosion. In other words, a clinically normal, or, shall we say, a benign-looking cervix. When one remembers that in these cervices the lesion may be

extremely tiny, and by that I mean microscopic in size, it becomes a problem to know how we can detect this kind of lesion. The answer is by the means of the vaginal and cervical smear, and I might say a word or two about these first of all, although I do not propose to discuss them in detail.

At the outset I would like to take issue with Dr. Hayden. He said that a cytologist has to do considerable study "just like a pathologist". I would add to that and correct him by saying that the cytologist should be a pathologist first of all, because the pathologist is ideally suited to study the changes in cells, since a large part of his training is based on the study of cells. There are far too many half-baked "cytologists" around, with resulting false positive reports and all the attendant trouble and worry to the patient that goes with such a report. A well trained pathologist can learn cytology in about three months of intensive training. We can, however, train "screeners", laboratory technicians, to process the large number of normal smears, recognizing the abnormals and putting them aside for somebody who knows something about cells to study and give a final verdict on.

In reporting the smears it is usual to grade them according to the system of Dr. Papanicolaou, the grading being from Class I to Class V, and I think it might be useful just to indicate what these various classes mean. Class I means a completely normal smear, Class II that the cytologist has seen in that smear some abnormal cells but that he does not consider these cells to be of either suspicious or malignant type. There are many different underlying causes responsible for the presence of Class II abnormal cells in smears but the important thing to remember is that such a smear can be ignored as far as the possibility of malignancy is concerned although it may indicate some other condition present, such as infection which might require therapy. A Class III smear is one in which the cytologist sees cells which are not certainly malignant, but which he feels are suspicious of the condition, and such a classification means that the red light is flashing and that smear should be followed up by a biopsy. A Class IV smear is a little more advanced than a Class III, and it means that the cytologist has seen cells in that smear which he thinks are almost certainly malignant, but he is not ready to stick his neck out completely. A Class V smear means that the cytologist has committed himself completely and that he is convinced that the cells he sees are definitely malignant cells. All of this simply means that from a Class III on up through IV to V, the patient should have a biopsy, and I want to emphasize that a positive smear report, whether it be a Class III, Class IV or Class V, must always be confirmed by biopsy. I would like to hammer that point home. All cytologic studies which are positive must have a biopsy to confirm the diagnosis.

I would like to say, too, that malignant looking cells may occur in conditions other than malignancy. Cells of Class III or suspicious type are seen particularly in the patient who has severe trichomonas infestation, and they may be seen in pregnancy and in chronic inflammatory diseases of the cervix. Usually the abnormal cells in such cases fall into Class III or Class IV, and this again, simply goes to prove the point that we must do a biopsy to prove the diagnosis.

The usefulness of the vaginal and cervical smear technique in detecting carcinoma in situ is indicated by studies in which, if we take a series of patients having proven carcinoma in situ, that is, proven by biopsy, in 80% of these cases a positive smear report will have been returned from routine smears. If in such a series the smears are reviewed critically following positive diagnoses from biopsy it is found that something like 95% of the patients with proven carcinoma in situ will have Class III or higher smears.

The first slide tonight (figure 1.) is that of a photo-micrograph of a cervical smear taken from the patient I am using to illustrate some of my points. This patient, a 44-year-old woman, went to consult her gynecologist for a routine check-up, and he told me that she had a completely nor-

mal looking cervix, and subsequently I was able to confirm his impression in the surgical specimen. The routine smear taken from this patient showed the presence of Class III, or suspicious cells.

The slide (figure 1) shows a picture of this smear under low-power and the large

FIGURE 1
Low-power view of vaginal smear showing malignant cells.

cells shown in the photograph, particularly the large one with the huge nucleus, are the abnormal cells which were reported as Class III.

The next slide (figure 2) is a high-power view of the same smear and shows the abnormal cells under higher magnification. It is not the point of this meeting tonight to go into cytologic details, suffice it to say

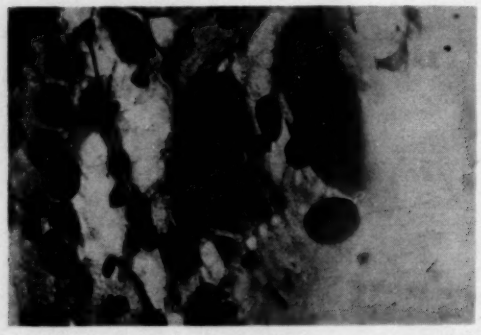

FIGURE 2
High-power view of field from figure 1 showing malignant cells in greater detail.

that these cells are highly abnormal, they have big nuclei, one being especially large, and all of these cells show deeply staining abnormal nuclei with prominent nucleoli, these being some of the features which we classify as abnormal.

Following this report the gynecologist preformed a biopsy, and at this point I might say a word about the biopsy in such cases. This is the typical case of a patient who had a positive smear and a normal looking cervix. From what area are you going to take the biopsy? There is only one satisfactory answer, and that is that the biopsy must be taken from the entire area where this possible cancer might arise. It is known that the most likely place for an early cancer of the cervix to develop is exactly at the point where the squamous epithelium of the ectocervix meets the columnar epithelium of the endocervix, in other words, at the squamo-columnar junction. Since the lesion may be microscopic in size, it is not sufficient to take random punch biopsies around the cervix. To be absolutely sure, the whole of the squamo-columnar junction should be taken, and this means doing a ring biopsy, excising the whole of the area. The responsibility then passes to the pathologist, and he must not be satisfied with taking small snippets of tissue from the biopsy material. He must cut it up into small pieces, block out the entire material, and then cut multiple sections from each block. The ideal would be to prepare serial sections, of course, but in ordinary routine work this is not feasible from an economic point of view, and multiple sections from each block provide a satisfactory compromise, and will reveal most lesions.

What is carcinoma in situ? I can best define it by saying that it consists of a lesion in which morphologically malignant changes are confined to a surface epithelium. In other words, the pathologist is relating morphologic changes in the cells of non-infiltrating epithelium with the changes he sees in the cells of frank infiltrative carcinoma. Carcinoma in situ is a contradictory term in itself, because by the term "carcinoma" we imply invasion of tissue stroma. Now, in carcinoma in situ we say this is carcinoma confined to surface epithelium, or lining epithelium, so here we have a contradiction in terms. The term is a poor one

but I think it is here to stay. Now, what are these morphologic changes? Well, they consist of changes both in the staining characteristics of nuclei, in the size and shape of nuclei, in the nuclear-cytoplasmic ratio, and in the relationship of cells within epithelium one to the other. The cells loose their normal relationships, this being referred to as loss of polarity. In squamous epithelium, the normal stratification, the normal maturing of the epithelium, is lost, and these changes are seen very well in the next slide showing material taken from the particular patient under discussion (figure 3).

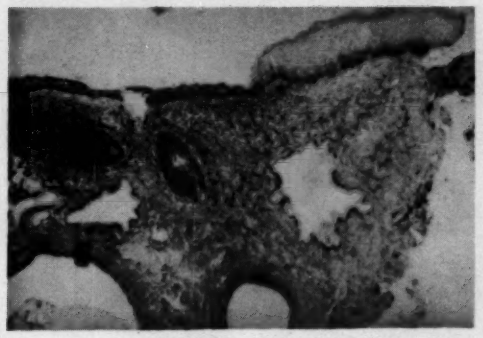

FIGURE 3
Low-power view of section of cervix showing normal squamous epithelium adjoining carcinoma in situ.

I have included in this section, as you can see, a piece of normal squamous epithelium from the cervix and in this the deeply staining cells of the basal cell layer can be seen, this is quite normal, the layer is an actively growing one and mitoses can be found there since the cells are reproducing, becoming more mature as they pass upwards towards the surface. In this process of maturation the nuclei become smaller, the cytoplasm of the cells becomes increased, and toward the surface the cells become cornified. In the section a sudden marked change in the appearance of the epithelium can be seen. The epithelium suddenly becomes much thinner and in this thinned epithelium the deeply staining cells are now seen at all levels from the basal cell layer to the surface, but you will notice that the lower limit of the epithelium is still definite and marked, being sharply demarcated from the underlying tissues, the cells in other words are confined to the surface. The astute observer, however, might say "Wait a minute, what is this down here?" These rounded clumps of deeply staining cells lying beneath the surface epithelium is definitely abnormal epithelium and could possibly be interpreted as infiltrating tumor tissue. Actually it is not, and I would ask you to note that in the section endocervical glands can be seen and these glands are actually responsible for the apparent infiltration we are looking at, a point I will explain in more detail in a short while when we look at the section under high-power.

The next slide (figure 4) is a picture of the surface epithelium from the previous

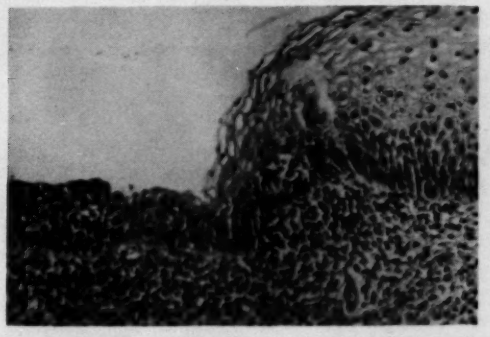

FIGURE 4
High-power view of junction of normal epithelium with carcinoma in situ.

slide taken under high-power and illustrates the epithelial changes in greater detail. On the right is the normal squamous epithelium showing the deeply staining basal cell layer, with the cells maturing as they get nearer the surface until on reaching the surface the nuclei are quite small and the epithelium well cornified. Quite suddenly there is an abrupt change and on the left of the slide we see, if I may use the term, "malignant", epithelium in which the deeply staining cells persist right to the surface of the epithelium. Many of these cells have abnormal nuclei with many mitotic figures being present and looking at this slide it is fairly easy to see why it is that in cancer in situ, just as in infiltrating cancer, we find abnormal cells in the vaginal smears. The abnormal cells extending directly to the surface of the epithelium desqumate and are shed off into the vaginal secretions and

since they have such abnormal characteristics they are recognizable in the smears.

The next slide (figure 5) is a still higher powered view of the abnormal epithelium to

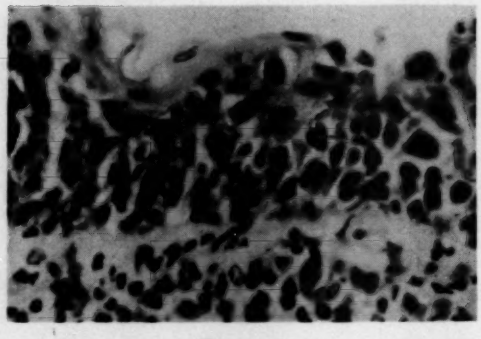

FIGURE 5
High-power view of carcinoma in situ illustrating changes in cell nuclei.

point out some of the abnormalities in the cells. Looking at this slide one sees markedly abnormal nuclei many being almost giant in type, and abnormal mitotic figures are present. I think that anyone with training in pathology, if given this piece of epithelium by itself, would say "This is malignant tissue." In other words, we have here malignant-looking epithelium confined to the surface.

The next slide (figure 6) is taken from a section of another area of the biopsy material, and here something else is happening. The same abnormal epithelium as before is present, but now it is dipping down into the underlying stroma and at first sight one might say that it represents beginning infiltration. Actually it is not. What is happening is that this actively growing epithelium, which has not yet penetrated into the stromal tissues but is growing rapidly, is following the path of least resistance. Before it bursts through the basement membrane and pressurizes itself into the underlying tissues, it will grow along established pathways, one of these pathways being that afforded by the openings of the endocervical glands. Just below the projecting epithelium in the slide, there is such an endocervical gland and I am sure that this gland actually communicates with the lesion seen in the section, and this epi-

FIGURE 6
Section showing carcinoma in situ growing into endocervical gland.

thelium is simply growing down into the endocervical gland, and a distinct basement membrane is still present around the abnormal tissue. At this stage the lesion is still intra-epithelial, or carcinoma in situ. It has not yet broken that important boundary, the basement membrane. As long as it remains confined to the glands or the surface epithelium it will probably not metastasize because the surface epithelium does not have lymphatic channels within it.

The final slide shows a high-power view of the portion of detached or apparently detached, portion of tumor tissue referred to previously in figure 3. In the upper part of the slide there is, again, the abnormal cancerous epithelium. Down below there is an apparently detached piece of similar appearing epithelium which might be interpreted as infiltrating tumor. Actually, it is not. This simply represents a piece of abnormal epithelium which has grown down into an endocervical gland, just as the fragment we saw in the previous slide was beginning to do. It has grown down deeply,

FIGURE 7
Section of carcinoma in situ showing lesion below surface in endocervical gland.

and because of the plane of the section it cannot be followed in the slide to the surface, but at the lower border of the tumor cells a few columnar epithelial cells can still be identified, and the epithelium still has a very distinct limiting membrane around it. At one time it was thought that such a lesion did represent early infiltration, but the majority of informed opinion at the present time regards such a lesion as representing carcinoma in situ.

The photo-micrographs have illustrated some of the histologic features upon which the pathologist makes his diagnosis. Now, in this particular case, the biopsy material contained the entire tumor as far as could be determined. The treatment this patient had, supplied the pathologist with the entire cervix for subsequent study, then it was cut up into a couple of dozen small pieces for blocking, and from these blocks multiple sections were cut, no residual tumor being found, so presumably the patient would have been cured in this case by a diagnostic ring biopsy. I would emphasize here that when a diagnosis of carcinoma in situ is made on a biopsy specimen, it simply means that the pathologist found carcinoma in situ in that particular specimen, and it must not be presumed that the patient only had carcinoma in situ from such material, because we know that very often these surface changes are associated with frankly infiltrating carcinoma. Such a finding is to be expected, since if it is believed that carcinoma in situ is the initial stage of infiltrating cancer, then in such cancers areas of carcinoma in situ adjacent to the frankly infiltrating tissue will be found from time to time.

Now a word or two about the nature of carcinoma in situ. Is it a true cancer? Unfortunately with the evidence that we have at the present time, there is no concrete proof on this point, but personally I believe that the evidence we do have is extremely suggestive, so much so that my own personal view is that carcinoma in situ does represent a stage in the development of a true cancer. Dr. Hayden has mentioned much of the evidence available already this evening. The age incidence of the lesion is one fact that may be mentioned, the peak incidence of carcinoma in situ tending to occur some ten years earlier than the peak incidence of frank infiltrating carcinoma of the cervix, a fact readily acceptable if, as is believed, carcinoma in situ represents an early slowly growing phase of development of truly infiltrating carcinoma. Carcinoma of the cervix in Jewish women is approximately five times less frequent as in the non-Jewish, and similarly carcinoma in situ is about one-sixth less frequent in the Jewish race. Similarly, infiltrating epidermoid cancer of the cervix is approximately twice as frequent in members of the Negro race as in the White race, and carcinoma in situ in the Negro is approximately twice as frequent as in the white race.

In some clinics series of cases of carcinoma in situ diagnosed by biopsy, have been watched without receiving any therapy following the biopsy, and they have subsequently developed infiltrating cancer. Dr. Hayden mentioned a series in Norway, and there is a similar series by Petersen in Den-

mark. Of Dr. Petersen's carcinoma in situ cases 25% have developed frankly infiltrating carcinoma anywhere from three to ten years after the initial diagnosis of carcinoma in situ, and perhaps more of them will as time goes on. At the Massachusetts General Hospital 700 cases which had histologic diagnoses of infiltrating carcinoma of the cervix or carcinoma in situ, were studied, and their past histories reviewed. Of these 700 cases, 13 were found to have had previous cervical biopsies anywhere from five to fifteen years before the final diagnosis was established. On reviewing the slides from the previous biopsies in these 13 cases it was found that 11 of them did in fact have evidence of carcinoma in situ in the earlier biopsy. This brings up another point, what were we calling carcinoma in situ ten, fifteen or twenty years ago? At that time the lesion was not diagnosed in the cervix although it must have been there as was proven by the Massachusetts General Hospital study. As I mentioned earlier, many cases of frankly infiltrating cancer of the cervix show associated changes of carcinoma in situ in adjoining surface epithelium, which might be interpreted as representing a change from the in-situ lesion to the infiltrating lesion.

All of the facts mentioned are suggestive but do not definitely prove the point, but I certainly believe that the lesion that is carcinoma in situ represents carcinoma in its earliest form.

Another point to be considered is that even though this lesion is an early cancer, can the changes regress — can the lesion heal? There are cases on record in which this seems to have happened, cases in which a diagnosis of carcinoma in situ had been made histologically with subsequent complete healing of the cervix and no recurrence of the lesion. Here again however we can not be absolutely sure because in such cases we have no means of knowing whether or not the biopsy did not remove the whole of the tumor, in other words, being, in effect, a curative biopsy.

DR. MORTON KEYSER:

Doctor Hayden and Doctor Abbiss have hinted around quite a bit as to treatment of carcinoma in situ of the cervix, and I think they both purposely left out anything about it because they knew I wouldn't have much to say as it is, and I don't want to get too involved in controversy.

When Doctor Abbiss said that in situ does not spread because of the absence of lymphatics, he gave us the crux of the treatment. The treatment is entirely dependent upon this fact. Therefore, the treatment can be entirely different from that of any invasive carcinoma which will spread by way of lymphatics and is very much more rapid in its progress, and of course, much more dangerous.

For purposes of practicality, I feel it is best to divide patients according to age groups. I think that it's difficult to say, but perhaps age 36 and over should be considered as one age group, and under 36 considered as a separate age group.

If a woman is 36 or beyond, and has had children, I feel that hysterectomy is the procedure of choice, for this, without question, eliminates permanently any possibility of recurrence, and, if this is truly a precursor to true invasive cancer, has eliminated this possibility. The hysterectomy does not need to be a radical hysterectomy for the simple reason that there is no invasion beyond the surface. There is no lymphatic spread. If it's true carcinoma in situ, definitely proven by multiple sections, large biopsy tissues taken, of course, then there need not be any radical procedure. TeLinde, in Baltimore, performs a modified radical hysterectomy. He takes everything but the lymph nodes.

If a woman is in this age group, then there are some who would amputate the cervix. This would bring us to discussion of that age group in between — the very young and the older women. A number of gynecologists would choose cervical amputation as the treatment in say age group 30 to 36, but this is still open to some question. It is possible that invasive carcinoma high in the cervix is present, and could be missed by simple amputation. I feel that although there are surgeons who

do it, that amputation of the cervix might be considered the unusual rather than the standard treatment.

The real problem in carcinoma in situ is not in the older group of women, but in the young woman who either has had no children or has perhaps one child, and in whom conservation of the childbearing function would be highly desirable.

The very nature of this disease is such, as Dr. Abbiss has said, that biopsy might readily cure the disease, and that would, of course, lead us right into the treatment of the condition by deep biopsy and conization or cauterization. There are great numbers of patients throughout the world who have been treated by this very simple method, most of whom are alive and only those, I feel, that perhaps are not with us today, are those who did not have true in situ carcinoma. As Dr. Abbiss implied, there are many patients in the past who had invasive carcinoma because it wasn't understood that this could be a surface condition, associated with deep invasive carcinoma that could easily be missed on the first biopsy.

As an illustration, I have in mind one of my own patients, who at age 21 had her first baby, and on her six months' postpartum examination I received a report from the pathologist of a Class II Papanicolaou slide, and biopsy proved it be in situ. I did a deep biopsy and conization and have been following the patient ever since, and subsequent smears have been negative.

The main point to stress, I believe, is that the treatment can be conservative in the sense that there need not be radiation or radical surgery.

PROGRAM

SIXTH ANNUAL SCIENTIFIC ASSEMBLY

DELAWARE ACADEMY OF GENERAL PRACTICE

Saturday, December 7, 1957

KENT MANOR INN, WILMINGTON, DELAWARE

9:00 A.M.	Registration.
10:00 A.M.	"Treatment of Hypercholesterolemia with Unsaturated Fatty Acids" — by J. A. Hubata, M.D., Kankakee, Illinois.
11:00 A.M.	"Recent Advances in the Chemotherapy of Leukemia and Related Disorders" — by Donald S. Searle, Ph.D., M.D., Tuckahoe, N.Y.
1:30 P.M.	"Management of Advanced Carcinoma with Radioactive Isotopes" — by Richard H. Chamberlain, M.D., Philadelphia, Pennsylvania.
2:30 P.M.	"The Allergic Patient, His Problems, Office Diagnosis and Treatment" — by Nathan E. Silbert, M.D., Chelsea, Mass.
3:30 P.M.	"A Rational Approach to the Management of High Blood Pressure" — by Edgar W. Young, M.D., Kalamazoo, Michigan.
6:00 P.M.	Cocktails & Dinner-Dance — Hotel Du Pont.

DIAGNOSIS OF VIRAL DISEASES AND EVALUATION OF PULMONARY FUNCTION

GEORGE J. BOINES, M.D.*

The first requisite for an accurate scientific early diagnosis of an infectious disease is the prompt identification of the etiologic agent.[1] Scientific developments in medicine today are progressing so rapidly that the busy clinician finds it difficult to keep pace with all the available tests which can be utilized to make possible an exact diagnosis early enough to stop or reverse the disease process by proper treatment. On the other hand, the clinician who does keep up with all of the tests finds that facilities are not available in the general hospital in a community like Wilmington where medical school teaching laboratories are lacking.

While it is true that our hospitals have expanded their physical structures, the laboratory and diagnostic facilities are always left trailing behind due to the forever-exhausted budget. Perhaps the responsibility for this insufficiency of modern diagnostic modalities rests on the shoulders of the physician. Hospital Boards and Administrators supply the medical workshop and it is up to us as physicians to see that the necessary tools of our profession are made available.

The laboratory has a contribution to make, which, if it should be adequately supported by state or community, will go far toward meeting the demands for modern medical care, and is capable of making that care predominantly preventive and of a high professional order.[2] In this presentation I wish to point out two examples of the many important diagnostic improvements which can be made in our hospitals.

The most recent medical advances which affect public health in general have been in the field of virus diseases.[3] This has come about since successful techniques were developed in isolating viruses[4] through tissue cultures. As a result of these new laboratory aids, the Salk[5] poliomyelitis vaccine was developed in 1954 for the immunization against three types of poliomyelitis viruses. These virus detection tests are no longer research procedures[6] but are practical and may be performed in any hospital laboratory.[7,8,9]

Another factor which makes viral diseases important from the standpoint of control is the inherent ability of viruses to vary[10] and to mutate.[11] New families of viruses have already been identified in the laboratory and clinical entities have been associated with them.[12,13] The ECHO[14] (Enteric Cytopathogenic Human Orphan), the APC[15] (Adenoidal-Pharyngeal-Conjunctival), the CA[16] (Croup Associated in Infants), the Coxsackie,[17] the AF[18] (Asiatic influenza virus) which is already producing a "hysteroid atmosphere" in our midst, and many others not as yet identified, are clinical problems. Early diagnosis by tissue culture and serological tests[19] is certainly essential if the diseases are to be treated intelligently and proper preventive measures taken to stop their spread.[20] Many conditions usually diagnosed clinically as summer diarrhea in children,[21] croup in infants, aseptic meningitis,[22,23] and influenzal meningitis, upper respiratory infections and conjunctivitis, non-paralytic or mildly paralytic poliomyelitis,[24] are in reality, infectious diseases caused by the new viruses. The following table from Kibrick et al[24] is self-explanatory.

Viruses Recovered in Tissue Culture from Stools of Patients with the Clinical Diagnosis of Poliomyelitis in Massachusetts in 1954

VIRUS	No. Recovered	Per cent
Polio	16	23.2
Coxsackie	5	7.2
Adenovirus	4	5.8
ECHO Type 2	2	2.9
ECHO Type 14	1	1.5
Unidentified	1	1.5
ECHO Type 6	40	58.0
TOTAL	69	100.0

* Chief in Communicable Diseases, St. Francis Hospital and Wilmington General Hospital Wilmington, Delaware.

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- Convenience—the low dose of 0.5 Gm. (1 tablet) per day offers optimum convenience and acceptance to patients

NEW DOSAGE

The recommended adult dose is 1 Gm. (2 tablets or 4 teaspoonfuls of syrup) the first day, followed by 0.5 Gm. (1 tablet or 2 teaspoonfuls of syrup) every day thereafter, or 1 Gm. every other day for mild to moderate infections. In severe infections where prompt, high blood levels are indicated, the initial dose should be 2 Gm. followed by 0.5 Gm. every 24 hours. Dosage in children, according to weight; i.e., a 40 lb. child should receive ¼ of the adult dosage. It is recommended that these dosages not be exceeded.

Tablets:
Each tablet contains 0.5 Gm. (7½ grains) of sulfamethoxypyridazine. Bottles of 24 and 100 tablets.

Syrup:
Each teaspoonful (5 cc.) of caramel-flavored syrup contains 250 mg. of sulfamethoxypyridazine. Bottle of 4 fl. oz.

[1] Nichols, R. L. and Finland, M.: J. Clin. Med. 49:410, 1957.

LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID COMPANY, PEARL RIVER, NEW YORK

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*Reg. U. S. Pat. Off.

There are no diagnostic viral facilities in Delaware. Consequently, many occasions have arisen in the past where specimens of blood, stool, spinal fluid, and throat washings were sent to Albany, USPH Communicable Disease laboratories at Montgomery, Alabama, Atlanta, Georgia, and to Philadelphia. Many times test tubes containing sera were broken in transit or became unsatisfactory so that weeks later it was necessary to recall the patient for additional blood. The results of these tests had been delayed two or more months, so that treatment of the patients was based on clinical evidence alone and the laboratory findings eventually confirmed or reversed the diagnosis.

Dalldorf[25] gives an excellent discussion on the planning for a virus laboratory in the general hospital.

He outlines the various tests in Chapter X entitled "The Simple Common Technics". The preparation of suspensions, antisera, inoculations of animals and eggs are discussed.

"The tests commonly used today in diagnosing viruses are (1) Cultivation of viruses in fertile eggs, tissue explants and monkey kidney or HeLa cells; (2) Neutralization test; basic serologic procedure in virology and yields by and large the most specific and significant evidence of the antigenic identity of viruses and of immune responses to infection; (3) Hemagglutination test: the most useful for studies of influenza and mumps in man and of Newcastle disease in poultry (this test has wide application in studies of individual patients and in field of epidemiologic surveys.); allantoic fluid of embryonated eggs successfully inoculated with throat washings from a patient suspected of having influenza will agglutinate chicken erythrocytes, indicating that a strain of virus has been isolated. The unknown virus is then identified by treating it with known antisera; (4) Complement fixation: used in the diagnosis of encephalitis, herpes simplex, influenza, lymphocytic choriomeningitis, lymphogranuloma venerium, mumps, psittacosis, Q-fever, Rocky Mountain spotted fever, typhus, and vaccinia."*

The additional laboratory space required for virology need not be more than two average rooms for incubators, centrifuge, refrigerators and work tables. The inclusion of virology in the regular hospital laboratory facilities of pathology, bacteriology, histology, chemistry, records, et cetera, will require additional trained personnel. Income derived from the virology tests will more than offset the added expense.

Another field of medicine in which outstanding progress has recently been made is in lung anatomy,[26] the application of pulmonary physiology to clinical problems of lung disease,[27] and pulmonary ventilation.[28] In pediatrics this is especially important, since Reichert states that "Abnormal pulmonary ventilation accounts for more than half the deaths during the first week of life".[29] According to Spencer[30] "In the classic mechanical and biochemical sense, normal respiration may be defined as the optimum adjustment of rate, depth, and pattern of breathing that meets the metabolic demand for oxygen uptake and carbon dioxide elimination with minimal expenditure of energy by the respiratory muscles". In order to detect the reason for abnormalities in oxygen intake and carbon dioxide elimination, one needs special equipment and trained personnel to use it. Here again our general hospital facilities are deficient.

Physiologists in anesthesiology[31] and in aviation medicine[32] have been able to analyze the process of respiration in great detail. They have developed respiratory equipment[33] which has been life-saving in high altitude flying and in such clinically important pulmonary diseases as pulmonary emphysema, pulmonary atelectasis, bronchial asthma, tetanus, obstructed airway in infants and adults (whether it be mechanical or paralytic), post-operative complications arising from anesthesia,[34] the pneumonias, respiratory acidosis and alkalosis,[35,36] and other pulmonary,[37] cardiac and paralytic[38] conditions in which there is interference with normal pulmonary ventilation.

* From Dalldorf, Gilbert, Introduction to Virology, 1955. Courtesy of Charles C. Thomas, Publisher, Springfield, Illinois.

Another disease in which the mechanics of respiration become important is bulbar respiratory paralytic poliomyelitis. Special "Respiratory Centers"[39] have been organized in hospitals in order to treat these patients efficiently. In Delaware, this work has been done at the Doris Memorial Unit of the Wilmington General Hospital.[40]

FIGURE 1
Photograph taken by the author at Doris Memorial Unit of Wilmington General Hospital.

Figure 1 shows a ten year old girl in the tank respirator. Child has paralysis of both upper extremities, intercostals, and one side of the diaphragm. The photoelectric cell is in position on the left ear. The Monaghan respiratory meter (resting on top of galvanometer) was used to measure the tidal air in order to regulate the adequacy of the negative pressure and rate of the respirator. The oxygen saturation of the blood was calculated by the galvanometer readings. The intermittent positive pressure machine attached to the oxygen tank is used to inflate the lungs at regular intervals. The average tidal air required is calculated by Radford's ventilation Nonogram.[41]

Figure 3 shows the use of the oximeter; photoelectric cell is attached to the patient's ear to measure oxygen saturation of the blood; galvanometers are on top of oximeter. Patient has tracheotomy for emergency suction of secretions.

The respiratory meter is an accurate instrument for measuring vital capacity. In patients with respiratory paralysis frequent vital capacity measurements are mandatory during the acute phase to determine when a respirator is necessary. When the vital capacity is reduced to less than 50% of the calculated normal[39] the patient must be placed in a respirator in order to prevent

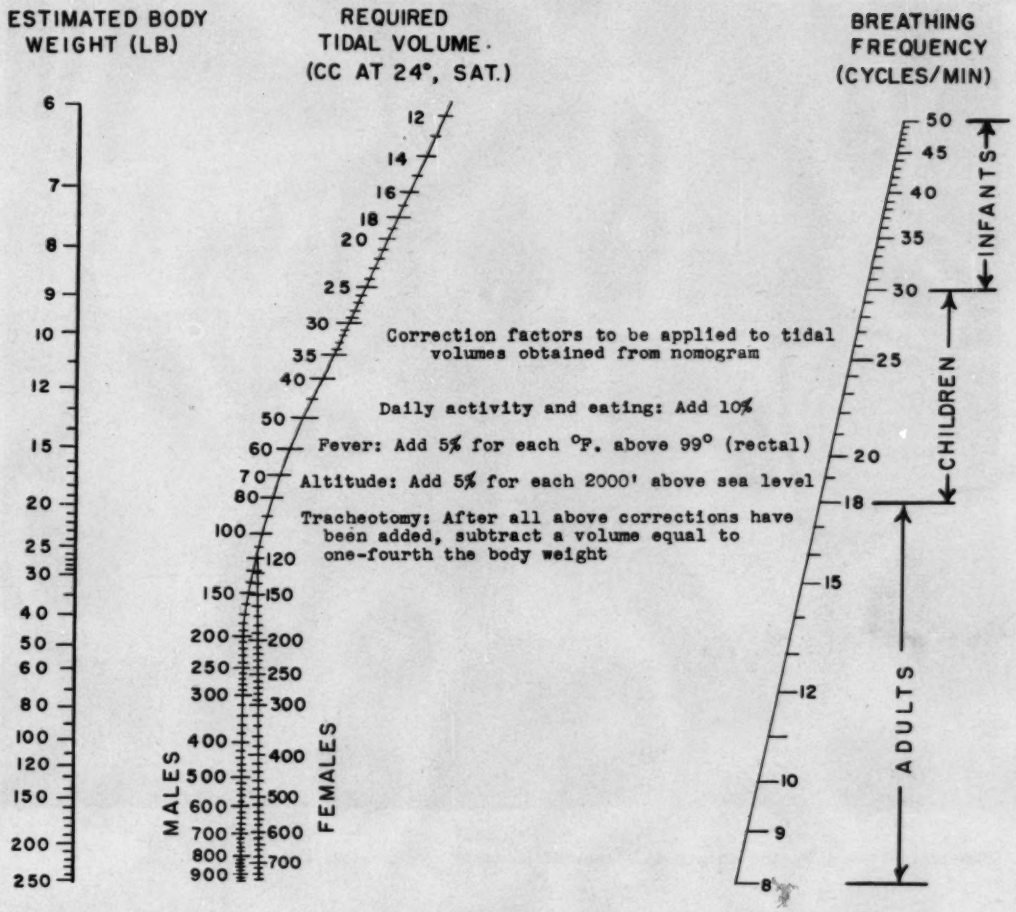

FIGURE 2
(Radford's ventilation Nomogram. Permission obtained from New England Journal of Medicine).

exhaustion and to prepare him psychologically and obtain his cooperation. The entire subsequent course of treatment may depend on this point because when patients are placed in the respirator late, or when respiratory acidosis has developed, the cooperation of the patient is poor and he becomes dependent on the respirator.

Special equipment and trained personnel require considerable funds. However, in this day and age when millions are spent in research, the problem of expense is a relative one. Life cannot be measured in monetary values. It is our responsibility to search constantly for better methods of diagnosis and treatment. To quote Bohan,[42] "Progress in any profession is measured by the amount of research done in it. Hospitals cannot progress unless they study themselves and seek methods of improvement. This is true in all areas of hospital activity, medical, education, nursing service, technical services, and hospital administration itself". Thus, it becomes the duty of the hospital clinical research committees to study the efficiency and the applicability of new tests and techniques and see that our patients and our community benefit from them.

SUMMARY

1. Viruses are now causing disease entities important to our patients and to the community as a whole. Diagnostic facilities are not yet available in the State of Delaware. Our virology problems can be solved

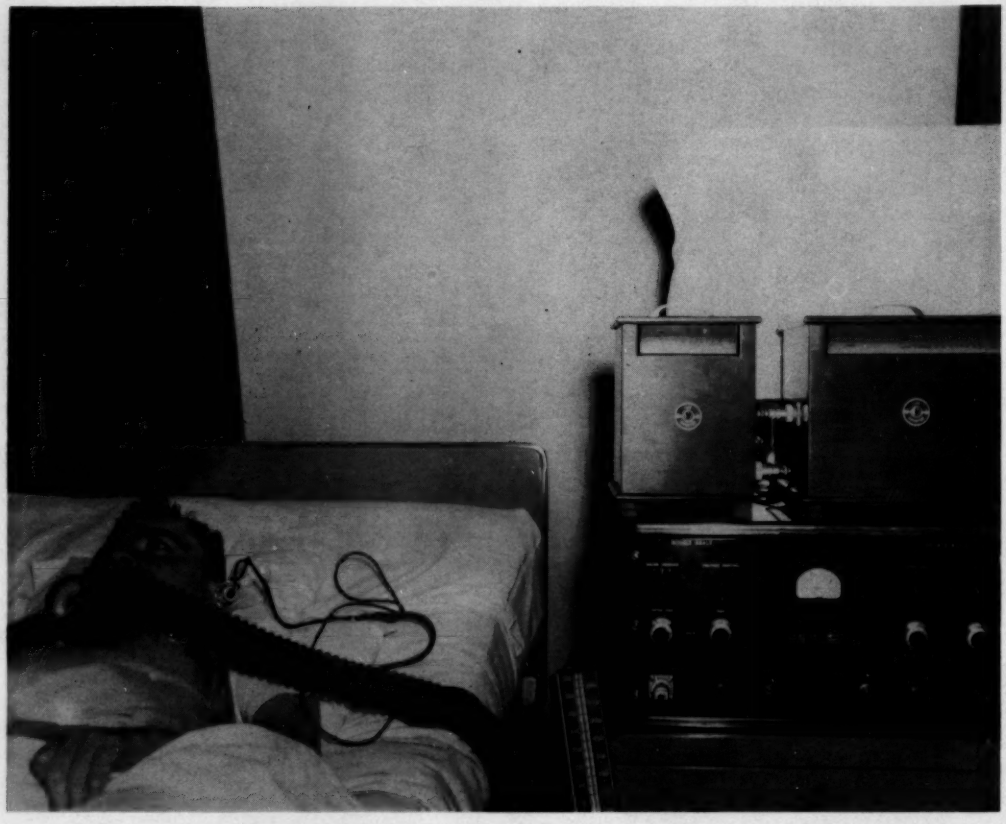

FIGURE 3
Photograph taken by the author at Memorial Hospital, Wilmington, Del.

by establishing facilities for the simple and inexpensive tests which are now available.

2. The physiology of respiratory function has been thoroughly studied and the findings have been applied clinically in aviation, also in respiratory paralytic poliomyelitis centers. Pulmonary function equipment and tests are essential in the armamentarium of the general hospital today in order to give scientific treatment to patients with lung and pulmonary ventilation problems. In many cases of abnormal pulmonary ventilation, oxygen administration is contraindicated. In other cases it is essential and life-saving when properly administered and supervised.

3. The importance of laboratory evaluation of viral diseases and of pulmonary ventilation abnormalities in the general hospital is emphasized. The former is not practiced inside Delaware. The latter is slowly developing in some of our hospitals, but the progress is tardy. The research has been done. It is now imperative that action be taken by staff, administration, and research groups, lay and medical, to expedite these facilities for the benefit of our patients and community.

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RESPIRATORY ALKALOSIS AND ASSOCIATED PHENOMENA*

JOHN J. GRAFF, M.D.**

An understanding of acid-base balance and electrolyte therapy can be significant in the preparation of the severely ill patient for the insult of anesthesia and surgery. Survival itself may depend on intelligent control of a critical postoperative state. One phase of acid-base balance is described in detail, with comparisons of related conditions. Calculations are used in an attempt to clarify the relationship of clinical and laboratory data.

Normal values applied to the Henderson-Hesselbalch equation illustrate the relationship between the carbon dioxide combining power (HCO_3^-), the dissolved carbon dioxide of the plasma (pCO_2) and blood pH.

$$pH = pK + \log \frac{HCO_3^-}{pCO_2} \quad 7.4 = 6.1 + \log \frac{27mE/L.}{1.35mE/L.}$$

Blood pH and the constant of other acid factors (pK) are expressed in negative log for convenience. Thus where a neutral solution such as water will have a hydrogen ion concentration of 0.0000001 gram per liter (1×10^{-7}) we represent this as pH 7. A solution ten times as acid (0.000001 gram or (1×10^{-6}) we designate pH 6. A solution one-tenth as acid is termed pH 8. Normal blood pH is alkaline, pH 7.4 and the constant is acid pH 6.1.

The normal ratio of HCO_3^- to pCO_2 is 20 to 1. Any increase or decrease of either value without a corresponding similar change in the other will disturb the value of pH of the plasma.

A clinical syndrome can now be examined with the help of the data already considered. Respiratory alkalosis is the state resulting when hyperventilation causes such a loss of carbon dioxide that the normal relationship with HCO_3^- is disturbed and alkalosis results. It is seen in a number of instances, examples of etiology being fever, anoxia, encephalitis and exaggerated physical activity. Typical values are substituted in the equation:

$$pH = 6.1 + \log \frac{24}{0.8} = 7.5$$

This early phase of uncompensated alkalosis is gradually changed when an increase of chloride, ketone acids and lactic acid results in a decrease of HCO_3^- to restore the normal ratio and normal pH.

$$pH = 6.1 + \log \frac{16}{0.8} = 7.4$$

This intermediate phase is termed a compensated respiratory alkalosis and progresses to a late stage in which there is further decrease of both HCO_3^- and pCO_2 to cause an acidosis similar in extent to a metabolic acidosis.

$$pH = 6.1 + \log \frac{6}{0.6} = 7.1$$

The differentiation between this late stage of respiratory alkalosis and metabolic acidosis could not be made from determination of the blood pH unless earlier stages had been observed. The markedly lowered pCO_2 would be of help in diagnosis because pCO_2 in metabolic acidosis is decreased to a lesser degree. Respiratory alkalosis exhibits neurological changes, as for example Chvostek's sign as seen in calcium tetany. A summary of points of differential diagnosis between respiratory alkalosis and metabolic acidosis is tabulated.

	RESPIRATORY ALKALOSIS	METABOLIC ACIDOSIS
pH early	increased	decreased
pH compensated	normal	decreased
pH late	decreased	decreased
ventilation	marked increase	some increase
PCO_2	marked decrease	some decrease
neurological	present	absent

The complete electrolyte study of the progression of a case of respiratory alkalosis shown:

* From the Department of Anesthesiology, St. Francis Hospital. Presented to the Medical Department, June 20, 1957.
** Chief, Department of Anesthesiology.

	Na	K	Cl	HCO_3^-	pH
Uncomp. Resp. Alk.	143	5.2	112	25	7.52
Comp. Resp. Alk.	122	5.3	100	16	7.42
End Stage Resp. Alk.	145	4.5	131	6	7.11

Attention is called to the sodium values that influence the resulting combined total of chloride and carbon dioxide combining power that are seen changing with the sodium determinations. The potassium change showing the characteristic decrease in late stages is typical of this condition. Other changes tabulated have already been discussed.

An illustration is given of a case of hepatic coma with electrolyte values before and after treatment.

	HCO_3^-	pH	K
pre-treatment	20mE/L.	7.69	2.4
post-treatment	21mE/L.	7.40	2.7

Seen in the equations:

$$pH = 6.1 + \log \frac{20}{0.4} = 7.69$$

and after treatment:

$$pH = 6.1 + \log \frac{21}{1.05} = 7.40$$

Comparison with values in treated metabolic acidosis is illustrative. In this case the only values available in the short period in which operation was delayed were the HCO_3^- values that showed the change from 13 mE/L. to 22 mE/L. The clinical appearance of the patient completed the picture, changing from an obviously dehydrated, cyanotic patient with skin cold and wet to one without dyspnea and with skin pink, warm and dry. Reconstructing equations here:

$$pH = 6.1 + \log \frac{13}{1.37} = 7.1$$

and after treatment:

$$pH = 6.1 + \log \frac{22}{1.37} = 7.35$$

A review of some other deviations of acid-base balance is included to further illustrate the buffer mechanisms. In a case of metabolic alkalosis from pyloric obstruction with vomiting and a marked loss chloride with a compensatory increased HCO_3^- we see:

$$pH = 6.1 + \log \frac{54}{1.35} = 7.6$$

The increase in HCO_3^- represents the effort to balance the sodium values that have declined less than chlorides. The effort to decrease respiration and increase pCO_2 and restore a normal ratio is not adequate because of onset of anoxia.

Another illustration of respiratory acidosis in which there is a marked increase in pCO_2 in emphysema:

$$pH = 6.1 + \log \frac{27}{3.0} = 7.0$$

Here there will follow selective retention of sodium and loss of chloride in urine to allow an increase in HCO_3^- to restore a more normal ratio and more normal pH. If this acidosis results from anesthesia, time will not allow correction by the kidneys.

In review, the physical condition of the patient and his history correlated with only the determination of HCO_3^- will allow diagnosis of acid-base imbalance. Thus in a patient with a history of diabetes with Kussmaul respiration, a low HCO_3^- will point to metabolic acidosis. In a patient with encephalitis with hyperpnea, a low HCO_3^- will mean respiratory alkalosis. An emphysematous patient with decreased ventilation and increased HCO_3^- will exhibit respiratory acidosis. A case of pyloric obstruction with vomiting and high HCO_3^- will be typical of metabolic alkalosis.

The treatment of respiratory alkalosis is outlined. Ten per cent carbon dioxide administered by catheter or tent is useful. The potassium and phosphate deficit should be corrected. If the original cause has not been removed, unusually large doses of intravenous sodium bicarbonate will be needed to help the late acidosis.

SUMMARY

Respiratory alkalosis is described by detailing the changes in the buffer systems of the body that result as it progresses. Physical findings and history are correlated with laboratory data. Calculations are made of this and other acid-base disturbances.

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PROCEEDINGS OF A MEETING OF THE SURGICAL DEPARTMENT OF ST. FRANCIS HOSPITAL

Moderator: JOSEPH F. HUGHES, M.D.*
Discussants: JOSEPH W. ABBISS, M.D.,**
EDWARD M. BOHAN, M.D.,*** RAFAEL E. ALZAMORA, M.D.****

This surgical conference was held in the Hospital Library on May 20, 1957. The agenda included the presentation of a case simulating acute appendicitis and comments on appendectomy.

DR. HUGHES:

We have an interesting case to present today, one of possible appendicitis. The patient had been in an automobile accident a few days before he came into the hospital, and then he had pain in the lower right quadrant, and when I examined him, he had tenderness and rebound tenderness, but fortunately he was not operated on. Dr. Alzamora, would you give the history?

DR. ALZAMORA:

The patient was a 16 year old boy, whose chief complaint was pain in the right lower quadrant and some nausea. His past surgical history included only a tonsillectomy in childhood. There was no family history of tuberculosis, diabetes, or heart disease; one aunt had cancer of the liver.

The patient stated that he was in a car accident April 5th and had hurt his right ankle. The night before admission, he had pain in the right lower quadrant, and felt nauseated. The pain was rather severe, but subsided a little on the morning of admission (April 8th). His bowel movements were normal and there were no urinary symptoms. Last summer, patient had the same kind of pain "off and on" for about a month.

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On physical examination the skin was very slightly jaundiced, especially on the face. The pupils were round and equal, and reaction to light and accommodation was normal. The corneae and sclerae were normal. There were no pathological findings in the neck. Marked dental caries were noted. The chest was normal in appearance. There was no cardiac enlargement, sinus rhythm was present, and there were no murmurs. The lungs were clear to auscultation and percussion. The abdomen was soft, and no masses were palpated. The liver, spleen, and kidneys were not palpable. There was slight tenderness in the lower right quadrant, but there was no abdominal guarding and no rebound tenderness.

DR. HUGHES:

When I examined him, I did find rebound tenderness. Dr. Alzamora reported that he didn't find any, but the temperature was normal, the pulse was normal, and his white count was within normal limits, so we chose to wait. The next day he developed jaundice. A prothrombin time was 67%. He was very tender over his liver, and I called Dr. Bohan to see him. Dr. Bohan, would you comment on this case?

DR. BOHAN:

The patient had a history of grippe-like symptoms and fever on April 5th and 6th, the two days prior to admission. In addition, he had pain in the right lower quadrant with nausea. A consultation was requested to determine the cause of the jaundice. There was a history of epistaxis the week before admission. The patient had one white stool. About two months before

admission, the patient had a tooth extracted and had received penicillin injections and also an injection of Novocaine. He had been complaining of vague abdominal pain for as long as eight months before admission.

On examination of the patient, marked dental caries were noted. The liver and spleen were both palpable and tender. The heterophile antibody reaction was positive in dilution 1:10, a normal reading. The differential count showed 66% polys and 34% lymphs. A total protein was 6.2, with the albumen 4, and the globulin 2.2. Alkaline phosphatase was normal at the time, reading 5 Bodansky units. The cephalin flocculation test was 3+ after 24 to 48 hours. A total cholesterol was 222 mg., blood urea nitrogen, 10, and blood sugar was 79 mgm. per 100 cc. of blood. At this time, the question of appendicitis was temporarily eliminated. The most likely diagnosis was hepatitis or homologous serum jaundice. The lowered prothrombin was very suggestive of liver damage. This test was repeated, and all readings were low. There was marked liver damage.

On April 19th, twelve days after admission, a re-examination of the patient revealed that some cervical and axillary nodes were present. A blood count done on the 18th showed a marked lymphocytosis, 70% lymphocytes. This brought up the question of leukemia or mononucleosis. The heterophile antibody test was above the level of the previous one, now reading 1:200. A level above 1:128 is definitely diagnostic. This confirmed the diagnosis of infectious mononucleosis.

The patient's liver and spleen were tender, and he was placed on treatment for liver disease.

He remained tender in the region of the appendix, and it was thought that he might have appendicitis or lymphadenitis in the region of the appendix. Mediastinal lymph nodes are also enlarged in mononucleosis. The disease is one of unknown etiology, evidently due to a virus, and the incubation period is five to fifteen days. Cervical nodes are usually prominent. The nodes vary from the size of a pea to a walnut, but are discrete and slightly tender. Differential diagnosis has to be made between infectious hepatitis, where one may get a lymphocytosis, tuberculosis, leukemia, Hodgkin's disease, and lymphosarcoma. In some cases, a sternal bone marrow or biopsy of the nodes may have to be done. It was hardly necessary here because the clinical course was good.

The existence of liver pathology in diseases not primarily hepatic is important to discover in all patients, medical or surgical. Sometimes the diagnosis can be made inversely by uncovering the liver disease first. In addition to the better known liver diseases, other ailments causing liver dysfunction are: heart failure, diabetes, rheumatoid arthritis, thyrotoxicosis, and infectious mononucleosis.

Infectious mononucleosis occurs most usually between 18 and 30 years of age. It is more likely to be found in males, and is rare in Negroes. Hepatomegaly occurs in 12%, and splenomegaly in 50%. Epistaxis is common. During the first few weeks, the heterophile antibody is not likely to be positive. In fact, it has been reported initially positive as long as eight to nine weeks after the onset. The appearance of jaundice here is very interesting because jaundice does not usually occur with mononucleosis. Only about 5 to 6% of these cases have jaundice.

Burns are known to cause liver damage. Spinal cord injury may also do so. Metastatic cancer and diseases of the gall bladder and ducts are almost too common to mention. Post-operative infections may cause liver damage.

Non-icteric hepatitis due to virus infection probably occurs more frequently than hepatitis with jaundice. Routine tests for bile in the urine are worthwhile, as bile may appear in the urine below the icteric level in the blood. Most an-icteric hepatitis will show a disturbed liver profile as a positive thymol turbidity or cephalin flocculation test.

When jaundice occurs in any patient, the case should be assumed to be medical, unless proven otherwise by classical surgical

symptoms and signs, and liver, blood, and urine tests confirm the diagnosis.

Schiff[1] has obtained a diagnostic accuracy of 92% with the combined use of clinical, laboratory, and needle biopsy of the liver. The needle biopsy is indicated only in the following situations:

a. To distinguish medical and surgical cases when classical symptoms and signs are absent and laboratory examinations are inconclusive.

b. To distinguish toxic hepatitis from infectious hepatitis where there is a history of exposure to a known hepato-toxic agent.

c. Obscure medical-systemic disorders.

d. Suspicion of metastatic neoplasm.

e. Hepatomegaly of undetermined cause.

The mortality with needle biopsy is less than 0.1%.

The prothrombin test is a sensitive index to the health of the liver cells. Lord and Andrus[2] state that every case of jaundice where the initial prothrombin time was 80% or more was extra-hepatic. Vitamin K is not absorbed adequately in the absence of bile acids. Only one-third of jaundice patients have an initial low prothrombin test.

This case is interesting because of the presence of appendicitis or lymphadenitis associated with the disease. Since the heterophile antibody reaction is not positive early in mononucleosis, it is quite possible to rush into surgery too soon.

It is my conclusion that this case demonstrates the great need for a thorough medical work-up before any patient goes to surgery. In some clinics in the country, all patients are admitted to the medical service. This might also be a mistake. However, it would seem very wise for the surgeon and medical man to consult before the operating room is called. In this situation, excellent judgment was shown by the surgeon in charge of the case.

The patient may have had appendicitis associated with the mononucleosis, but the symptoms and signs of the disease gradually subsided. He is still being studied for a possible recurrence of appendicial disease.

DR. ABBISS:

I haven't seen any deaths from infectious mononucleosis, and I believe they are quite rare. In fact, you can't find a good account of the pathology from autopsy material even in the literature. I would like to say a word about the heterophile antibody test that Dr. Bohan mentioned.

This is a very valuable test; it's a test for an antibody found in a certain percentage (I think about 80%) of these infectious mononucleosis patients and this antibody has the property of agglutinating sheep's red cells. Now, it does occur in other diseases, for example, in serum sickness, and I should mention the fact that when you get a raised titre, and anything over 1:56 is to be regarded as abnormal, that does not say the disease is infectious mononucleosis, and to get a better indication, one should request then a differential agglutination test of Davidshon's (Chicago).

In this test, we first absorb the serum with beef red cells and also with guinea pig kidney, and the point here is that if we have a true heterophile antibody of infectious mononucleosis, the antibody will not be absorbed by the guinea pig kidney more than one tube back, whereas, with the beef cell, it will be completely absorbed. So let's say for example, you have a titre reported of positive in 1:112. You request the absorption test (and that is quite a low titre, incidentally), and we find then that after absorption with the beef red cell antigen, there will be no agglutination, no titre. With the guinea pig, it may drop back to 1:56, but that would be regarded as a postive test. In most cases, the titres go far higher, and after the antibody absorption, it should perhaps drop back a tube or a couple of tubes of the guinea pig kidney and be completely absorbed by the beef red cells.

Now this differential testing is reversed in other diseases, but we won't go into that. That kind of result with a raised titre is specific for infectious mononucleosis. The other thing we might say about this disease

is, of course, the abnormal cells that one finds in the blood, some very frequently. This disease is important because of this feature. Often a patient has a sore throat, nodes in the neck, an enlarged spleen, and one gets a report of abnormal lymphocytes. Of course, the first thing one thinks about is leukemia, particularly since the disease occurs so often in young people.

The cells are very abnormal, and to the unpracticed eye, they may be diagnosed as leukemic cells; they may be called lymphoblasts, for example, but a person with experience can usually pick them out, and, indeed, suggest the diagnosis, simply by examination of a blood smear, when these abnormal cells are present, and in the classical case, one will have both abnormal cells and the heterophile antibody. I think that in any case of abnormal cells in childhood, one should certainly have a heterophile antibody test done, even though a diagnosis of leukemia has been made from the smear. Sometimes, the count goes up around 100,000 white cells in this disease; it can be a dead-ringer for leukemia.

DR. HUGHES:

This case presented was a problem in diagnosis. On the day of admission, he had a condition compatible with appendicitis. In doubtful cases, it is wise to observe a patient for 24 to 48 hours and very often the developing clinical picture will confirm or rule out the diagnosis of appendicitis. For this patient, an operation may well have proven disastrous in view of his damaged liver. Thus, at times, acute appendicitis may be a difficult diagnosis to make.

The operation of appendectomy is only about two centuries old. In reviewing the subject, I find that the first appendectomy was done over 220 years ago in 1735 by an Englishman, Dr. Claudius Amyand[3] at St. George's Hospital. This was reported in the Philosophical Transactions of the Royal Society, and this appendix was found in a draining hernial sac. During the operative procedure, he found the appendix and tied off the base. The patient was cured; the drainage of pus completely stopped. The operation didn't take over a half hour. The hernia recurred. This patient was an 11 year old boy.

The first appendectomy done in this country was done by R. N. Hall in 1886 at the Roosevelt Hospital in New York.[4] Dr. John B. Deaver had this comment to make: ". . . That a knowledge of the pathology of the vermiform appendix slumbered, nay, even hibernated, from the time of Melier in 1827, who cites the work of Amyand 92 years earlier, until the day of Fitz, is one of the most remarkable things in the whole history of medicine".

Cantrell[5] of Johns Hopkins says that 20% to 25% of normal appendices in patients with pre-operative diagnosis of acute appendicitis should not be looked upon as an unreasonable figure, but a necessary evil. The mortality of appendicitis involves first of all, the mortality of general anesthesia, and this runs 0.08%. In unperforated appendices in a collected series of 5,676 cases, the mortality was 0.23%. In perforated cases (also reported from Johns Hopkins from 1928 to 1931) there were 85 cases, and they had a 19% mortality. From 1947 to 1954, they had 219 cases and they had a 3% mortality.

Dr. Abbiss, do you have something to say about normal appendices?

DR. ABBISS:

The question of normal appendix is always a difficult one; it puts the pathologist on the spot. I don't report them as normal, I just report them as "vermiform appendix". That's non-committal, and doesn't put me on the wire, and obviously, if we are going to make a flat statement "this appendix is normal", we'd have to examine the whole thing end to end by multiple sections.

There has been some work out recently by Rudy Schenken from Omaha, in which he's described focal appendicitis: very small areas of ulceration with tiny inflammatory exudates attached to the ulcerated area within the lumen of the appendix, and this apparently can give rise to symptoms. We have found some of that kind of appendicitis, and, on one occasion, a well known

surgeon was quite shocked when I found it. He swore the appendix was normal, which is rather a reversal of what one usually has to do. This has one important point, and that is if we're going to find these minimal cases, the lead we get when examining the specimen grossly is by the presence of maybe a little bead of pus, and if the surgeon opens the appendix in the operating room that inflammatory exudate may be washed off, and it may wash away the only clue the pathologist has, because he sees no abnormality, he simply takes random sections.

Incidentally, I make a practice of taking a section from every appendix, whether it's apparently normal or not, from the tip and from somewhere along its lumen. I know some men don't bother to do that; if it looks normal, they call it normal, but I do take a section just to have something for the record. In these minimal cases, it's important not to open the appendix and look at it, no matter how great the temptation is, in the operating room. Incidentally, I always take an opened appendix as a bad sign, the last resort, taking the appendix to try and find out where the inflammation was. To me, acute inflammation means edema, dilatation of blood vessels, the presence of polymorphonuclear leukocytes, and so on, in other words, all the cardinal signs, histological signs, of an acute inflammatory process. Less than that I do not recognize. I don't recognize "subacute appendicitis"—I recognize resolving acute appendicitis. Chronic appendicitis I never report.

DR. HUGHES:

As Dr. Bohan pointed out, the prothrombin test is a very sensitive one, and the details must be carefully followed. Dr. Abbiss, how often should the reagent for determination of prothrombin time be made up?

DR. ABBISS:

The reagent should be made up freshly every day. . . . The test has a very tricky end-point, and ideally, in a given institution, it should be done by the same person every day, if you're going to get reproducible results. That often, unfortunately, is impossible. You may get variations there. We're using the Symplastin technique here which is perhaps the most simple. It avoids the making up of two solutions.

(Other members of the Surgical Department entered into the discussion.)

DR. HUGHES:

This meeting today points up the fact that even though appendicitis is a common condition the surgeon must always be wary of operating on a patient with a serious condition which can best be treated medically.

I wish to thank those present for their interest and thorough coverage of the agenda.

N.B. Recently, an appendectomy was done for apparent recurrent appendicitis. At this time, the patient's liver had returned to normal size. The van den Bergh direct reaction was slightly positive. There was 1.0 mg. of bilirubin. The heterophile antibody reaction was positive in dilution 1:50 and the prothrombin time was normal. The sedimentation rate was normal and a complete blood count showed a predominancy of lymphocytes over the segmented polymorphonuclear leukocytes. Evidently the mononucleosis has not quite subsided.

(The Surgical Staff wishes to thank Miss Ann Moran for her able assistance in compiling this material).

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THE ADMINISTRATION OF TRYPSIN BUCCALLY IN THE TREATMENT OF INFLAMMATION AND EDEMA*

JOSEPH M. MILLER, M.D., GEORGE C. GODFREY, M.D.,
MILTON GINSBERG, M.D. and CONSTANTINE J. PAPASTRAT, M.D.

Trypsin in aqueous solution produces beneficial results when it is given intramuscularly to patients with inflammation and edema[1]. Innerfield[2,3,4] reported that trypsin administered buccally seemed to provide a simple and an effective method for instituting physiologic processes that resulted in subsidence of edema and other signs of acute inflammation. A tablet was designed to permit slow absorbtion since it was felt that a better effect might be achieved in this manner. The results of treatment were excellent. About one-third of the patients who were treated with such a tablet complained of a tingling sensation along the edge of the tongue or at the site of the buccal application. This complaint was much less severe on the second day of treatment and was practically gone on the third day. A zone of erythema of mild degree appeared often at the site of the application. Treatment had to be discontinued in only two patients because of soreness of the mouth.

The severity of the effects produced by trypsin upon a mucous membrane may be conditioned by the size of the dose and the time it remains at the site before complete absorption occurs. Accordingly, soft tablets containing 2.5 mg. of trypsin were prepared upon the premise that if disintegration of the tablet was rapid, absorption of the enzyme would be accelerated, and the pain and redness of the mucous membrane would be prevented. The supposition was correct for beneficial results were obtained from the use of trypsin in the treatment of inflammation and edema without side effects.

Initially, 2.5 mg. of trypsin were administered every twelve hours for a minimum of three days, and for longer if the status of the clinical condition of the patient demanded it. Subsequently, the patients were given 5 mg. every twelve hours, and later, 5 mg. four times during the hours in which they were awake.

The patient must be carefully instructed how to take the enzyme. The tablet is placed in the buccal pouch and should dissolve in about two to five minutes. The patient should not expectorate and should not swallow the saliva for about five minutes after the tablet has dissolved. The trypsin should not be retained for a period of time longer than five minutes or soreness and redness of the mucous membrane of the mouth will follow. The tablet should not be swallowed since the enzyme will be destroyed by the acid secretions of the stomach.

The empiric observations that profound changes can be produced in inflammation and edema by the administration of trypsin buccally has not been explained by chemical investigations. Trypsin activates plasminogen in the euglobulin fraction of the blood serum to plasmin[5-9]. Plasmin lyses fibrinogen and fibrin. At the present time, the key factor in the reversal of inflammation and edema seems to be the proteolysis induced by plasmin. Apparently, the micro-chemical environment of the involved area is modified sufficiently so that circulation to the site is improved and a greater delivery of the humoral antibodies and of the administered antibacterial drugs occurs. The net results are a regression of the inflammation and an abatement of the edema.

The fact that chemical reactions are reversible may provide a hypothesis for the action of plasmin in the reversal of inflam-

* From the Surgical Service, Veterans Administration Hospital, Fort Howard, Maryland.

mation and edema. A chemical system which has the capacity to regain its balance exits at all places in the body. When an imbalance is created by an exogenous force, as in the presence of inflammation and edema, macromolecular substances, such as partially polymerized molecules of fibrin, may be deposited in the interstitial tissues. This event may be due to a failure of delivery of the proper proteolytic enzyme to the involved site or its presence in insufficient amount to depolymerize large molecules. This enzyme may be of systemic or of local origin. At the present time, the origin of the enzyme is only of academic importance. It is known that fibrinogen and plasminogen are closely associated for it is difficult to prepare fibrinogen free from plasminogen. All that may be necessary at the involved site is the presence of an activator for plasminogen. A conversion of the zymogen to the enzyme occurs and proteolysis is initiated. If this occurs, the cellulitis will disappear. If digestion of the macromolecular substances does occur, the area becomes isolated from the surrounding tissues by the inflammatory membrane. The necrotic debris in the loculated site is digested by enzymes, which are derived from bacteria, leukocytes, and tissues to form pus.

Forty-four patients with various conditions were treated with trypsin buccally. The dosage of trypsin was varied and the best results were obtained when the patients were given the largest dose used, 5 mg. four times a day during the hours in which they were awake.

Thirty-three patients with infections of various types including two with infections associated with gangrene due to arteriosclerosis were treated with trypsin buccally. Twenty-three patients obtained an excellent result, five good, three fair, and two poor. The two patients with gangrene had a poor result due to a bad blood supply to the involved area.

Eleven patients were given trypsin buccally to prevent the edema which usually follows operations about the head and neck. Nine patients had an excellent result, one good, and one fair. This aspect of the use of proteolytic enzymes has not enjoyed the acceptance to which it is entitled. Where edema is allayed or prevented, healing will be more rapid, and improved cosmetic results will follow.

Forty-three of the forty-four patients treated did not have any side effects from the administration of trypsin buccally. One patient complained of burning in the mouth when the trypsin was given. An area of redness in the mucous membrane was present where the tablet lay during the period of absorption. An investigation revealed that the patient had a lower denture to which the trypsin became adherent and thus the enzyme was incontact with the mucous membrane for a period longer than that which was recommended. Hemorrhage, hematomas, and petechiae were not seen. Some of these patients were pretreated with trypsin for two days before operation and normal clotting of the blood was seen at the time of operation. Three of the patients, who were receiving 5 mg. of trypsin four times a day during the hours in which they were awake, had prothrombin times done and their blood tested for fibrinolysis. The prothrombin times did not change significantly from the normal ones. Fibrinolysis was not observed during the period of observation which was three days.

Results may be improved when trypsin is used prophylactically by starting the drug at least two days before the time of the contemplated operation. When such treatment cannot be given and the patient cannot take trypsin buccally during the period immediately after the operation, trypsin in an aqueous solution should be injected intramuscularly. This can be followed by the administration of the enzyme buccally when the patient can cooperate in taking the drug.

The administration of trypsin buccally modifies the inflammatory barrier about an area of infection. Healing substances may pass more easily into the involved area but bacteria and their products may pass outward at the same time. All patients who are treated with trypsin buccally for in-

(Continued on page 308)

Editorials

CANCER DETECTION

It is fitting that the subject of cancer detection be reviewed in this issue of The Journal with its symposium on cancer.

Ten years have passed since the establishment of a Cancer Detection Center (CDC) in this state. Its aims and limitations were described in The Journal for August, 1947. Briefly, the aim of the CDC is to make the early diagnosis of cancer while it is still localized and curable. Admittedly, certain obscure cases will be missed. Certainly, persons with any signs or symptoms should not be seen in the CDC but should go to their private physician. The CDC is for apparently healthy persons, not for patients suspected of having cancer.

A Diagnostic Clinic, on the other hand, examines *patients* who are suspected of having cancer. There, the examination is more thorough and also more costly. Clinics of this type estimate their per capita cost to be five times that of the CDC. Withall, certain obscure cases are still missed.

When the CDC finds evidence to justify a tentative diagnosis of malignancy (lump in breast; positive cervical smear; etc.) and when these findings have been transmitted to the private physician, its job is done.

How, then, can the CDC fail in attempting to reach its stated goal? Such failures are few and limited to the occasional obscure case which also might be missed by a more thorough and extensive examination.

How does the entire cancer detection program fail the person who has submitted to examination? The most common cause is the complacency of the private physician — a tendency to procrastinate and "sit tight" for awhile. Many physicians tend to play the law of averages — the Class III cervical smear that *probably* means nothing and the lump in the breast that *probably* is benign. True, many Class III smears are benign but the only way to be *certain* in the individual case is by microscopic examination of an *adequate amount of tissue.* Likewise, the lump in the breast is never benign until the lump itself has been examined microscopically.

The CDC is here to help you help your patient. It has done its part of the job well — let us do ours.

flammation or edema should be given one of the antibacterial drugs to prevent the possible spread of infection.

SUMMARY

Trypsin given buccally produces a modification of the inflammatory reaction and the absorption of edema. Treatment with trypsin given buccally must be accompanied by the administration of an antibacterial drug. The use of trypsin buccally is not a substitute for sound surgical treatment. Further investigation of the use of trypsin buccally is indicated.

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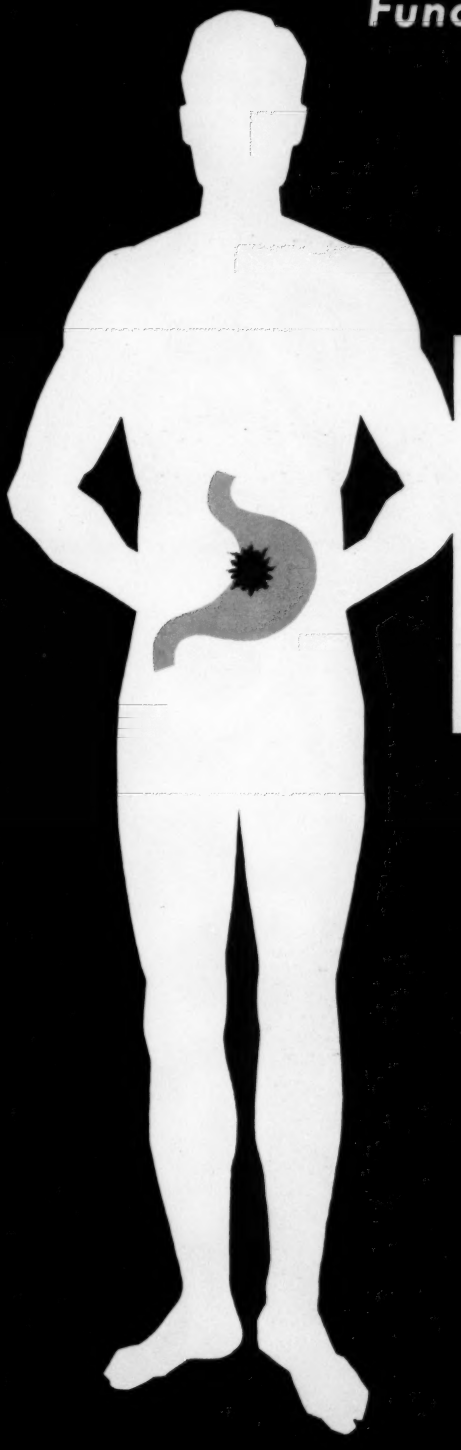

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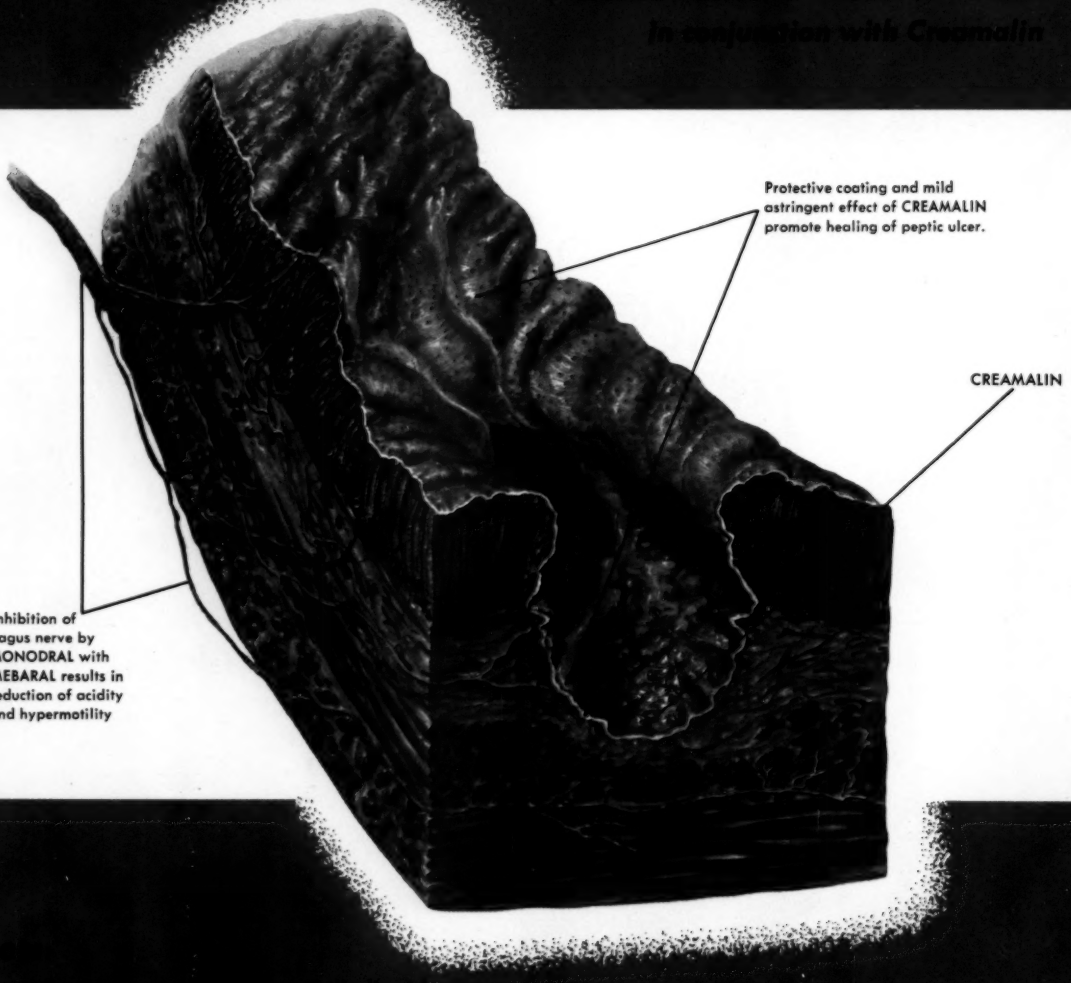

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1. Rusek, H. L.: J. Am. Geriat. Soc. *4*:877 (Sept.) 1956.

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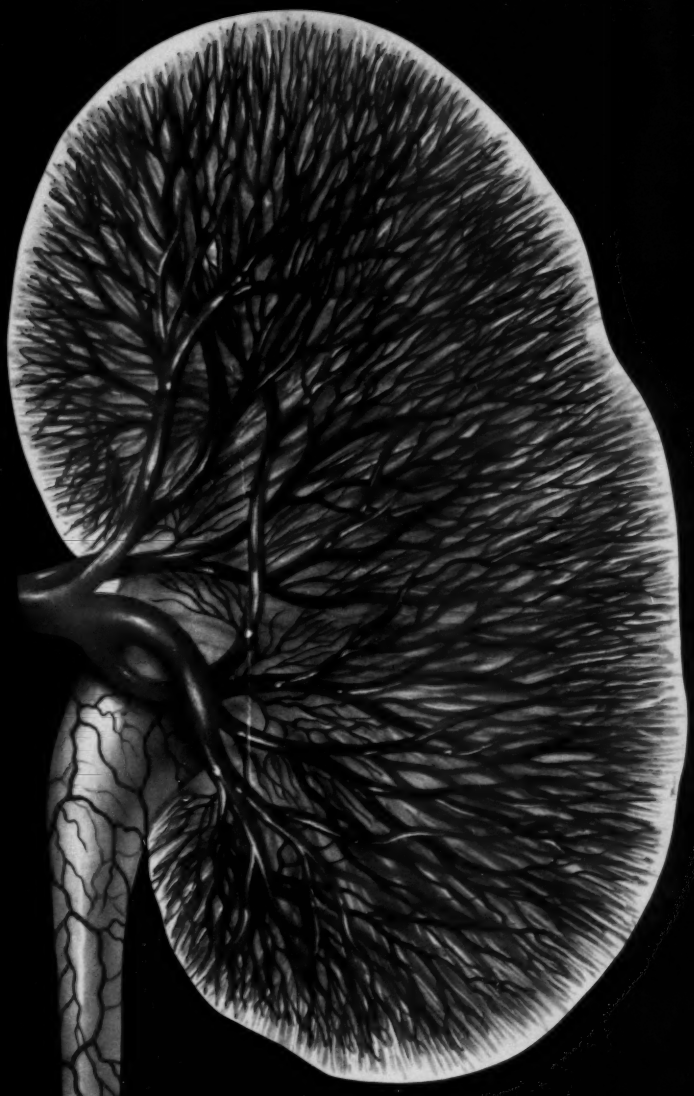

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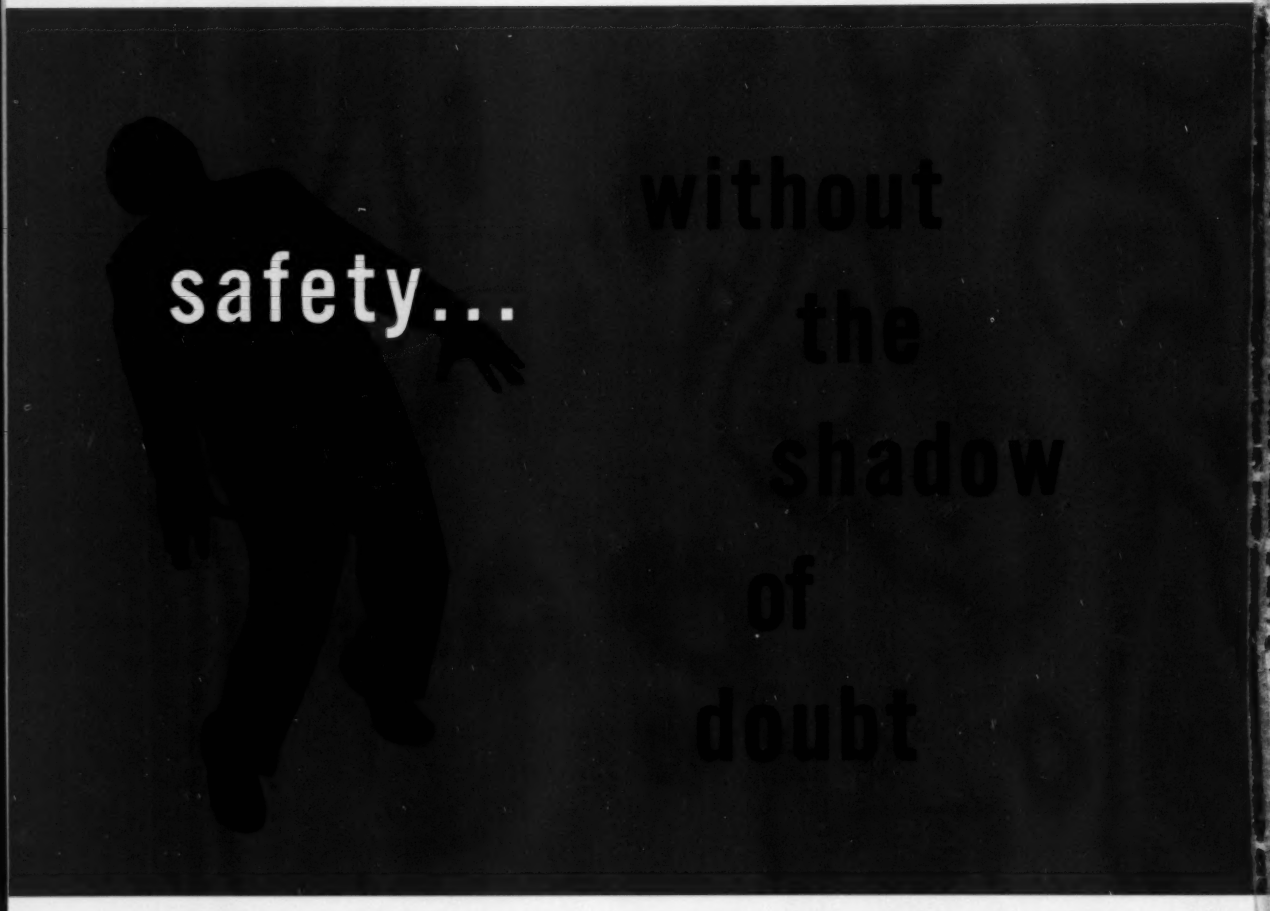

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ARALEN® *in* RHEUMATOID ARTHRITIS

Extensive studies of rheumatoid arthritis and related collagen diseases—in this country and abroad—have shown the antimalarial Aralen phosphate to be highly effective and well tolerated in a large percentage of patients.

Clinical Results with Aralen in Rheumatoid Arthritis

Author	No. of Cases	Major Improvement	Minor Improvement	No Effect
Hoydo[1]	28	22	5	1
Rinehart[2]	25	12	4	9
Freedman[3]	50	43	3	4
Bagnall[4]	108	77	12	19
Bruckner[5]	36	32	0	4
Cohen and Calkins[6]	22	17	3	2
Schorbel et al.[7]	25	9	8	8
Total	294	212 (72%)	35 (12%)	47 (16%)

- Success dependent upon persistent treatment
- Often of benefit where other agents have failed
- Remissions on therapy well maintained
- Remission of 3 to 12 months possible even if treatment is interrupted
- Tachyphylaxis not evident

GENERAL EFFECTS:

- Patient feels better
- Patient looks better
- Exercise tolerance increases
- Walking speed and hand grip improves

LABORATORY EFFECTS:

- E. S. R. may fall slowly
- Hemoglobin level may gradually rise

ANALGESICS AND STEROIDS:

- Requirements usually reduced or eliminated

JOINT EFFECTS:

- Pain and tenderness relieved
- Mobility increases
- Swellings diminish or disappear
- Muscle strength improves
- Rheumatic nodules may disappear
- Even severe or advanced deformity may improve
- *Active* inflammatory process usually subsides
- Joint effusion may diminish

DOSAGE:

Aralen is cumulative in action and requires four to twelve weeks of administration before therapeutic effects become apparent.

Latest information indicates that an initial daily dose of 250 mg. of Aralen phosphate is preferable to the higher doses sometimes recommended. However, if side effects appear, withdraw Aralen for several days until they subside. Reinstate treatment with 125 mg. daily and, if well tolerated, increase to 250 mg. The usual maintenance dose is 250 mg. daily.

New Chemotherapy

INDICATIONS:

- Rheumatoid arthritis, acute or chronic —with or without adjunctive therapy.
- Spondylitis
- Arthritis associated with lupus erythematosus or psoriasis

THEORY OF ACTION:

Aralen appears to suppress or induce remission of rheumatoid inflammatory processes by inhibiting adenosinetriphosphatase.

HOW SUPPLIED:

Aralen phosphate: 250 mg. tablets in bottles of 100 and 1000.
125 mg. tablets in bottles of 100.

Tolerance:

Aralen is usually well tolerated. Toxic effects are usually mild and to date have been transitory in nature, disappearing completely either on continuance or cessation of therapy or on reduction in dosage.

Gastrointestinal disturbances (e.g. nausea, rarely vomiting, diarrhea, abdominal cramps, anorexia) are frequent manifestations of intolerance. Temporary blurring of vision (due to interference with accommodation) is also relatively frequent.

Pleomorphic skin eruptions (e.g. lichenoid, maculopapular, purpuric), although generally mild, may preclude the use of an optimum dosage schedule. If a skin reaction persists on a reduced dosage schedule, or recurs after reinstitution of treatment with gradually increasing doses, discontinue Aralen till the lesion again disappears and consider resuming treatment with Plaquenil® (brand of hydroxychloroquine).

Less frequently transitory vertigo, headache, lassitude, or neurological disturbances, such as nervousness, irritability, emotional change, and nightmares have been reported. Instances of unexplained slight gradual weight loss as the patient's general health and arthritic condition improved have been mentioned. Occasional instances of bleaching (depigmentation) of the hair have been described.

Although an occasional instance of leukopenia, with normal differential count, has been reported (WBC about 3000), it has not proved troublesome because it has always been reversible on discontinuance, or diminution of the dose. Even spontaneous reversal may occur while full dosage is maintained.

Caution:

Aralen is known to concentrate in the liver and, although hepatic damage has never been reported, the drug should be used with caution in the presence of liver disease. In the presence of severe gastrointestinal, neurological, or blood disorders, the drug should be used with caution or not at all. If such disorders occur during the course of therapy, the drug should be discontinued. Concomitant use of gold or phenylbutazone with Aralen should be avoided because of the tendency of these agents to produce drug dermatitis.

Clinical Comments:

Of fifty patients receiving Aralen therapy, "43 have become really well; that is, they have no stiffness, and any pain that occurs can reasonably be attributed to use of joints affected by secondary degenerative changes. They have no evidence of joint inflammation, but may have a raised erythrocyte sedimentation rate. They have little or no need for analgesics." *Freedman*[3]

"One hundred and twenty-five private patients have been carefully followed clinically and haematologically while receiving well over 200 patient-years of chloroquine [Aralen] therapy. The results are considered good in 70%, one-half of these cases being in remission. Improved work performance, sedimentation rate, and hemoglobin levels paralleled the major objective gain in this 70%. 90% of them remained on chloroquine [Aralen] therapy, half for more than two years. Classical peripheral rheumatoid arthritis, spondylitis, arthritis of juvenile onset, and rheumatoid disease with psoriasis, all appeared to respond about equally well.

"It is suggested that chloroquine comes closer to the ideal for long-term, safe, control of rheumatoid disease than any other agent now available." *Bagnall*[4]

"Out of the 36 rheumatoid arthritis cases we treated . . . favorable results were obtained in 32 cases. *Bruckner et al.*[5]

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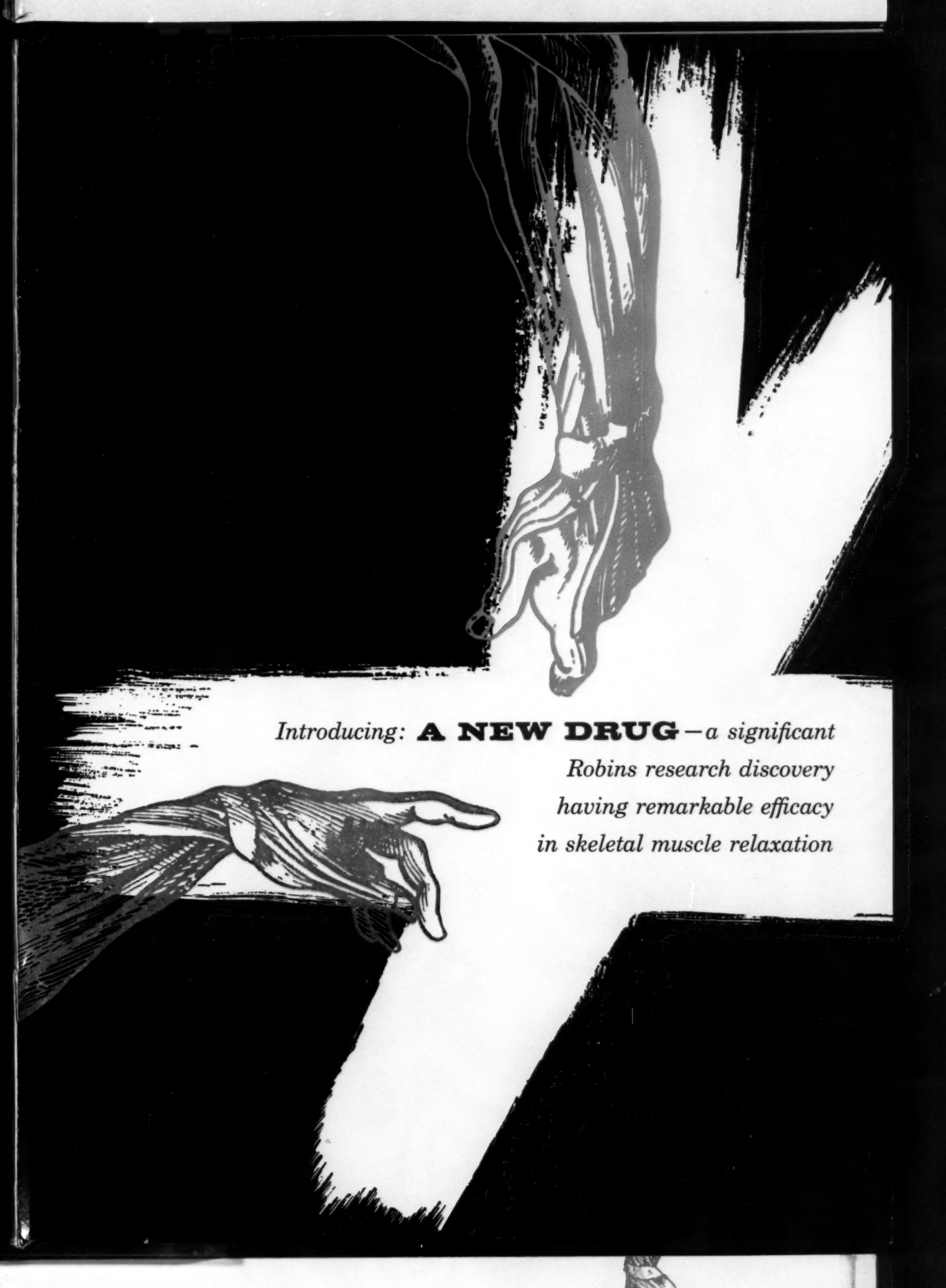
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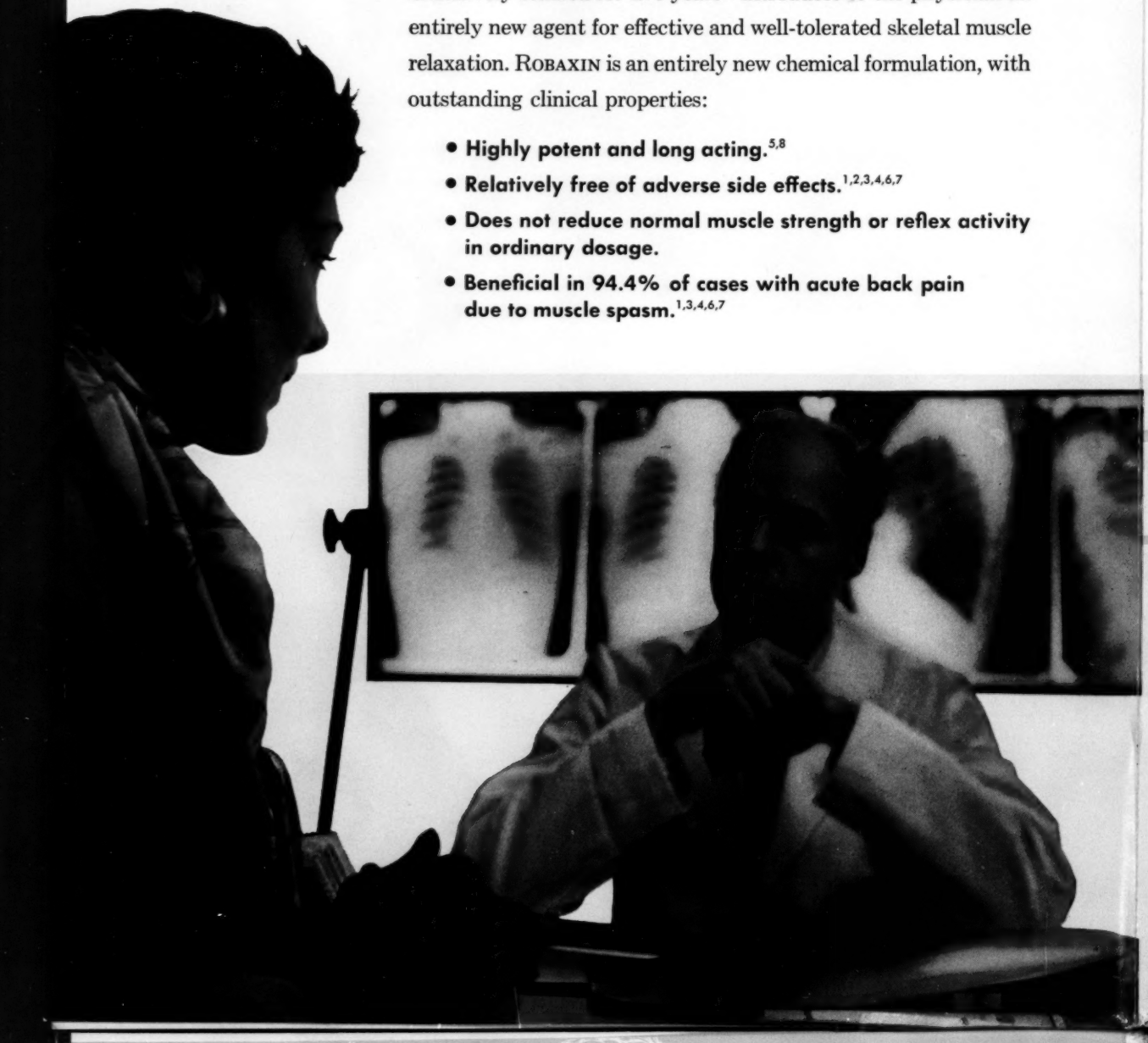
- **Relatively free of adverse side effects.**[1,2,3,4,6,7]
- **Does not reduce normal muscle strength or reflex activity in ordinary dosage.**
- **Beneficial in 94.4% of cases with acute back pain due to muscle spasm.**[1,3,4,6,7]



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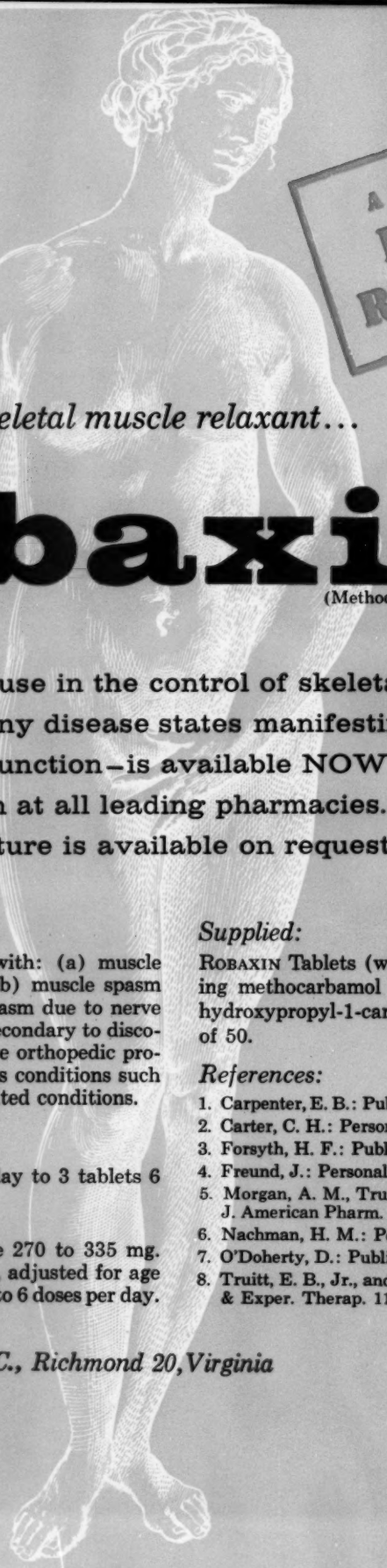
When tested in 72 patients with acute back pain involving muscle spasm, ROBAXIN induced marked relief in 59, moderate relief in 6, and slight relief in 3 – or an over-all beneficial effect in 94.4%.[1,3,4,6,7] No side effects occurred in 64 of the patients, and only slight side effects in 8. In studies of 129 patients, moderate or negligible side effects occurred in only 6.2%.[1,2,3,4,6,7]

CLINICAL RESULTS WITH ROBAXIN IN ACUTE BACK PAIN[1,3,4,6,7]

Disease entity	*No. of Cases*	*Duration of Treatment*	*Dose per day (divided)*	*Response*				*Side Effects*
				Marked	*Mod.*	*Slight*	*Neg.*	
Acute back pain due to								
(a) Muscle spasm secondary to sprain	18	2-42 days	3-6 Gm.	17	1	0	0	None, 16; Dizziness, 1; Slight nausea, 1.
(b) Muscle spasm due to trauma	13	1-42 days	2-6 Gm.	8	1	3	1	None, 12; Nervousness, 1.
(c) Muscle spasm due to nerve irritation	5	4-240 days	2.25-6 Gm	4	1	0	0	None, 5.
(d) Muscle spasm secondary to discogenic disease and postoperative orthopedic procedures	30	2-28 days	1.5-9 Gm.	24	3	0	3	None, 25; Dizziness, 1; Lightheadedness, 2; Nausea, 2.*
Miscellaneous (bursitis, torticollis, etc.)	6	3-60 days	4-8 Gm.	6	0	0	0	None, 6.
TOTAL	72			59	6	3	4	

*Relieved on reduction of dose



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Acute back pain associated with: (a) muscle spasm secondary to sprain; (b) muscle spasm due to trauma; (c) muscle spasm due to nerve irritation; (d) muscle spasm secondary to discogenic disease and postoperative orthopedic procedures; and (e) miscellaneous conditions such as bursitis, torticollis, and related conditions.

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ADULTS: 2 tablets 4 times a day to 3 tablets 6 times a day.

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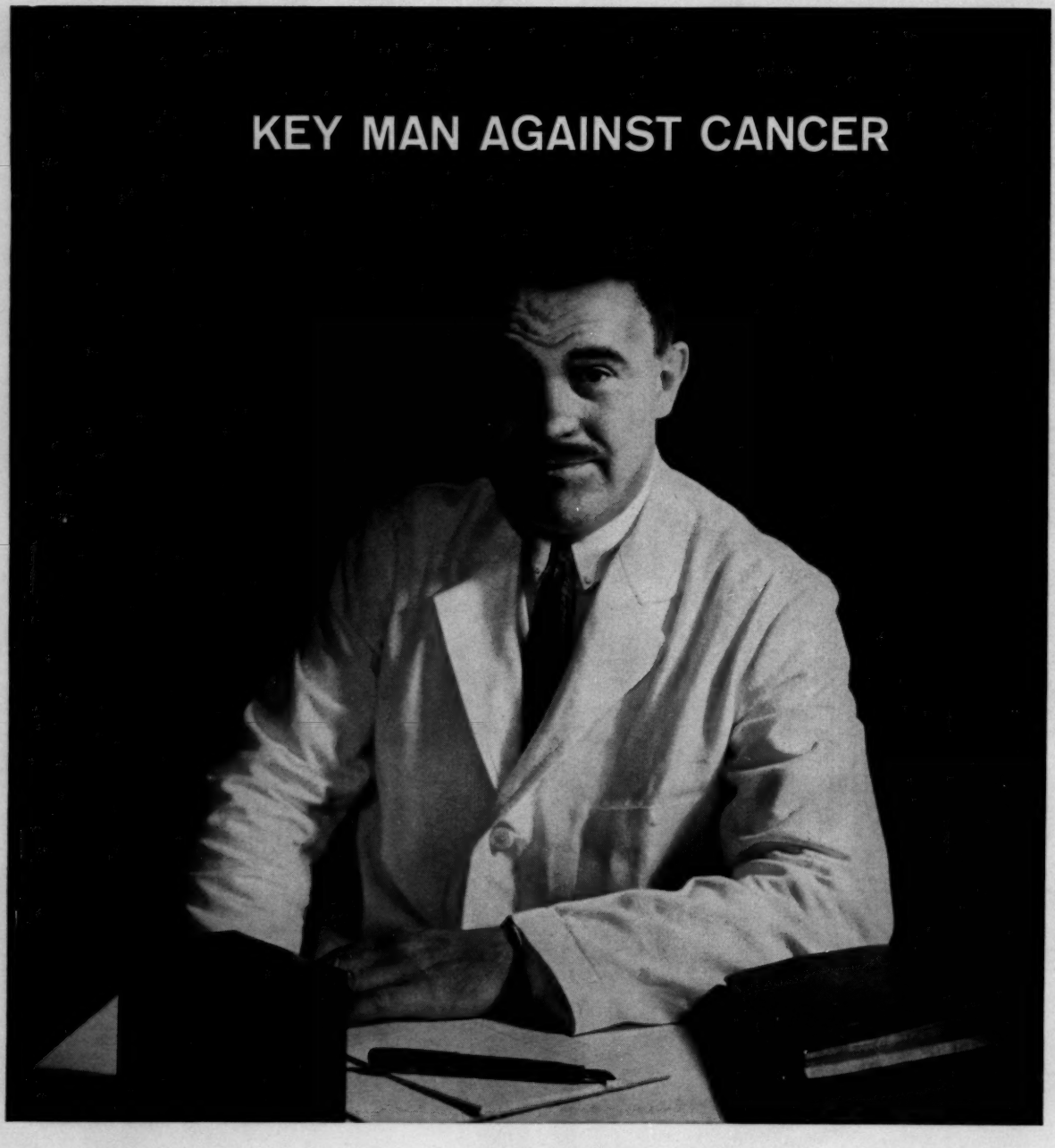

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